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SUDDEN DEATH AND LIFE-THREATENING VENTRICULAR ARRHYTHMIAS IN CARDIAC SARCOIDOSIS AND GIANT CELL MYOCARDITIS

A NATIONWIDE OUTCOME STUDY WITH ASPECTS OF DIFFERENTIAL DIAGNOSIS

KAJ EKSTRÖM

DOCTORAL DISSERTATION
Doctoral Program in Clinical Research

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"Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less."

Marie Curie (1867–1934)

To Pinja

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Ekström K, Lehtonen J, Hänninen H, Kandolin R, Kivistö S, Kupari M. Magnetic Resonance Imaging as a Predictor of Survival Free of Life-Threatening Arrhythmias and Transplantation in Cardiac Sarcoidosis. *J Am Heart Assoc.* 2016;5: e003040. doi: 10.1161/JAHA.115.003040.

II Ekström K, Lehtonen J, Kandolin R, Räisänen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. *Eur J Heart Fail.* 2016;13: doi: 10.1002/ejhf.606

IIb Ekström K, Räisänen-Sokolowski A, Lehtonen J, Kupari, M. Long-term outcome and its predictors in giant cell myocarditis. Letter regarding the article "Long-term outcome and its predictors in giant cell myocarditis." *Eur J Heart Fail.* 2020;22:1283–1284. doi: 10.1002/ejhf.1953

III Ekström K, Lehtonen J, Kandolin R, Räisänen-Sokolowski A, Salmenkivi K, Kupari M. Incidence, Risk Factors and Outcome of Life-Threatening Ventricular Arrhythmias in Giant Cell Myocarditis. *Circ Arrhythm Electrophysiol.* 2016;9:pii: e004559 doi: 10.1161/CIRCEP.116.004559

IIIb Ekström K. Update: Re-evaluation of the diagnosis of giant cell myocarditis. Online commentary, Dec 20, 2020.

IV Ekström K, Lehtonen J, Nordenswan HK, Mäyränpää MI, Räisänen-Sokolowski A, Kandolin R, Simonen P, Pietilä-Effati P, Alatalo A, Utriainen S, Rissanen TT, Haataja P, Kokkonen J, Vihinen T, Miettinen H, Kaikkonen K, Kerola T, Kupari M. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. *Eur Heart J.* 2019;23:pii: ehz428. doi: 10.1093/eurheartj/ehz428.

V Ekström K, Räisänen-Sokolowski A, Lehtonen J, Nordenswan HK, Mäyränpää MI, Kupari M. Idiopathic giant cell myocarditis or cardiac sarcoidosis? A retrospective audit of a nationwide case series. *ESC Heart Fail.* 2020;28. doi: 10.1002/ehf2.12725.

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ABBREVIATIONS

AAD	Anti-arrhythmic drug
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
AF	Atrial fibrillation
AHA	American Heart Association
ARVC	Arrhythmogenic right ventricular cardiomyopathy
AV	Atrioventricular
AVB	Atrioventricular block
CAD	Coronary artery disease
CI	Confidence interval
CMRI	Cardiac magnetic resonance imaging
CS	Cardiac sarcoidosis
CT	Computed tomography
DCM	Dilated cardiomyopathy
ECG	Electrocardiography
EGM	Intracardiac electrogram
EMB	Endomyocardial biopsy
ESC	European Society of Cardiology
GCM	Giant cell myocarditis
HF	Heart failure
HR	Hazard ratio
HRS	Heart Rhythm Society
hs-cTnT/I	High-sensitivity cardiac troponin T/I
ICD	Implantable cardioverter defibrillator
IL	Interleukin
JCS	Japanese Circulation Society
JMHW	Japanese Ministry of Health and Welfare
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MIDFIN	Myocardial Inflammatory Diseases in Finland
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association functional class
PVS	Programmed ventricular stimulation
RFCA	Radiofrequency catheter ablation
RV	Right ventricle
RVEF	Right ventricular ejection fraction

SCD	Sudden cardiac death
SVA	Supraventricular arrhythmia
TH	T-helper
TNF	Tumor necrosis factor
UNOS	United Network for Organ Sharing
VA	Ventricular arrhythmia
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WASOG	World Association of Sarcoidosis and Other Granulomatous Diseases
^{18}F-FDG PET	^{18}F-fluorodeoxyglucose positron emission tomography

ABSTRACT

The aim of this study was to study the role of sudden cardiac death (SCD) and life-threatening ventricular arrhythmias (VA) in cardiac sarcoidosis (CS) and giant cell myocarditis (GCM), and to investigate the clinicopathological relationship between these diseases.

CS is the cardiac manifestation of sarcoidosis, a systemic disease of unknown etiology. The hallmark of sarcoidosis is the non-caseating granulomatous inflammation seen in affected organs. GCM is a rare myocardial inflammatory disease characterized by widespread myocardial destruction, eosinophilia, and giant cells in the absence of granulomas. Clinically significant VAs are common in both CS and GCM and sometimes SCD is their first manifestation. For this study, all CS and GCM patients detected both from the national research register and from the cause-of-death register from 1998 until the end of 2015 were included. Additionally, clinically manifest cases of GCM from 1991 to 1998 were included. Hospital charts, autopsy reports, and histological material were reviewed and cardiac magnetic resonance imaging (CMRI) studies for a subpopulation of 59 CS patients were analyzed.

The study included 351 cases of CS and 29 cases of GCM. The detection rate of both diseases increased over the study period. Female predominance was seen in both CS and GCM. At the time of presentation, the mean age of CS and GCM patients was 52 and 57 years, respectively. The spectrum of manifestations was similar in both diseases. The most common clinical presentation was atrioventricular block in CS and heart failure in GCM. SCD was the first sign of myocardial disease in 14% of cases in both the CS and GCM cohorts. The role of SCD as the mode of death was substantial in both diseases: it accounted for four out of five fatalities in CS and nearly half in GCM.

Over half of the cases originally diagnosed as GCM were converted to CS after reevaluation, most commonly due to missed myocardial granulomas or misclassification as GCM, despite recognition of cardiac or extra-cardiac granulomas. Lifetime symptomatic CS patients with an initial diagnosis of GCM had a better five-year transplant-free survival (46%) compared to “true” GCM patients (27%), but the groups did not differ with regard to cumulative incidence of SCD.

The 10-year survival in lifetime-diagnosed CS patients was 87%. Several CMRI parameters were associated with worse transplant-free survival free of VAs. These included higher late gadolinium enhancement extent, lower right ventricular ejection fraction and thinning (< 4mm) of the basal interventricular septum.

In GCM, the five-year overall and transplant-free survival rates were 67% and 26%. At least moderate necrosis or fibrosis on myocardial biopsy and elevated N-terminal pro b-type natriuretic peptide were predictive of worse transplant-free survival. The highest risk of life-threatening VAs was seen during the first year after symptom onset. The cumulative incidence of SCD or any life-threatening VA rose to 52% at 12 months after symptom onset and was associated with at least moderate fibrosis on myocardial biopsy and higher cardiac troponin at presentation.

In conclusion, SCD and life-threatening VAs have a major role in the clinical course of many CS and GCM patients. Clinically and histopathologically, CS and GCM share many similarities and their differential diagnostics can be challenging.

TIIVISTELMÄ

Tutkimuksen tavoitteena oli selvittää sydänperäisen äkkikuoleman ja henkeä uhkaavien kammioperäisten rytmihäiriöiden yleisyyttä sydänsarkoidoosissa ja jättisolumyokardiitissa. Tavoitteena oli myös tutkia näiden sairauksien kliinis-patologisia yhtäläisyyksiä.

Kliinisesti merkittävät kammioperäiset rytmihäiriöt ovat yleisiä sekä sydänsarkoidoosissa että jättisolumyokardiitissa ja joskus sydänperäinen äkkikuolema on näiden sairauksien ensioire. Tätä tutkimusta varten keräsimme tiedot sydänsarkoidoosi ja jättisolumyokardiittipotilaista vuodesta 1991 vuoden 2015 loppuun. Tietoja kerättiin sekä kansallisesta tutkimusrekisteristä että -kuolinsyyrekisteristä.

Tutkimus koostui 351 sydänsarkoidoosi- ja 29 jättisolumyokardiittipotilaasta. Ensioireet olivat samankaltaisia molemmissa tautiryhmissä, mutta eteiskammiokatkos oli yleisin löydös sydänsarkoidoosissa ja sydämen vajaatoiminta jättisolumyokardiitissa. Sekä sydänsarkoidoosi- että jättisolumyokardiitiryhmässä sydänperäinen äkkikuolema oli taudin ensimmäinen oire 14% tapauksista. Äkkikuolema oli kuolinmekanismina neljässä viidestä sydänsarkoidoosin aiheuttamasta kuolemasta ja lähes puolessa jättisolumyokardiitissa.

Yli puolet alun perin jättisolumyokardiitiksi diagnosoiduista potilaista paljastui uuden evaluaation jälkeen sydänsarkoidoosiksi. Yleisimmin granuloomia ei oltu tunnistettu alkuperäisessä patologisessa tutkimuksessa tai tunnistamisesta huolimatta tapaus luokiteltiin jättisolumyokardiitiksi. Alun perin jättisolumyokardiitiksi klassifioitujen sydänsarkoidoosipotilaiden 5-vuotisennuste ilman sydänsiirto oli parempi verrattuna jättisolumyokardiittipotilaisiin.

Sydänsarkoidoosissa elossaoloennuste elinaikana diagnosoitujen potilaiden osalta 10 vuoden kohdalla oli 87%. Sydämen magneettitutkimuksessa todettava laaja-alainen jälkitehostuma, alentunut oikean kammion ejektiofraktio ja kammioväliseinän ohentuma olivat huonoja ennusmerkkejä.

Jättisolumyokardiitissa elossaoloennuste 5 vuoden kohdalla oli 67% ja elossaoloennuste ilman sydänsiirtoa oli 26%. Henkeä uhkaavien kammioperäisten rytmihäiriöiden insidenssi oli korkein ensimmäisen vuoden aikana. Sydänlihasbiopsian löydökset sekä sydämen biomarkkerit taudin alkuvaiheessa olivat merkittäviä ennusteeseen ja rytmihäiriöriskiin assosioituvia tekijöitä.

Yhteenvetona, henkeä uhkaavat kammioperäiset rytmihäiriöt ja äkkikuoleman riski muodostavat merkittävän kliinisen ongelman sekä sydänsarkoidoosissa että jättisolumyokardiitissa. Sydänsarkoidoosi ja jättisolumyokardiitti muistuttavat toisiaan sekä kliinisesti että histopatologisesti ja niiden erotusdiagnostiikka voi olla haastavaa.

1 INTRODUCTION

Sarcoidosis is an inflammatory disease characterized by granulomatous inflammation in virtually any organ.[1] Of all possible organ involvements, cardiac sarcoidosis (CS) is the most malignant manifestation and is associated with impaired survival.[2] Giant cell myocarditis (GCM) is a rare inflammatory cardiomyopathy and early studies depicted it as a very aggressively progressing disease with high rates of mortality and cardiac transplantation.[3,4] Later studies have suggested that the disease spectrum might be broader and that modern therapeutics may improve survival.[5–7]

CS and GCM share clinical and histopathological features.[4] Heart failure (HF) is the most common presenting clinical manifestation of GCM,[3,6] whereas high-grade atrio-ventricular (AV) conduction disturbances are typically the most prominent first signs of clinical CS.[8,9] The occurrence of sudden cardiac death (SCD) and life-threatening ventricular arrhythmias (VA) (sustained ventricular tachycardia (VT) and ventricular fibrillation (VF)) are common in both CS[9–12] and GCM.[3,4,6,13] In CS, sustained VT or VF can be the main presenting manifestation in 33% of cases[9] and early studies combining autopsy and clinical registries of CS reported SCD as the main presenting clinical manifestation in 11–17% of cases in CS.[14,15] In GCM, life-threatening VAs have been reported as first manifestation in 14 to 32% of cases.[3,4,6] The long-term arrhythmic risk is also significant in both diseases.[3,6,11,13,16,17] It is thus obvious that the treatment of life-threatening VAs and the prevention of SCD present major challenges in both CS and GCM. VAs are mostly linked to re-entry associated with myocardial scarring,[18–21] but other arrhythmic mechanisms, e.g., those linked to active inflammation, play a role as well.[22–26] There are no in-depth analyses of life-threatening VAs in GCM and data on their true incidence is limited. Knowledge is based on incidental case reports and a few small series[3,5,6,13] reporting outcome-data regarding VAs. In CS, numerous contemporary studies do report SCD figures in CS,[9,11,12,27–30] but they all suffer from the limitation that mostly only symptomatic, lifetime identified patients were studied, masking the true frequency of SCD in CS.

The Myocardial Inflammatory Diseases in Finland (MIDFIN) study group, focusing on the research of CS and GCM, was established in 2008 and a nationwide registry of CS and GCM patients was set up. My research in the MIDFIN group started in 2013. Life-threatening VAs in CS and GCM constitute the main theme of my thesis. I set out to study their incidence and predictors, as well as to describe the overall prognosis of these diseases in the era of modern HF-, anti-arrhythmic- and immunosuppressive therapy. During the work I also focused on the relationship and differential diagnostics of CS and GCM.

2 REVIEW OF THE LITERATURE

2.1 Etiology and pathogenesis

2.1.1 Sarcoidosis

Sarcoidosis is a disease characterized by the presence of inflammatory non-caseating epithelioid granulomas in diseased organs. Sarcoidosis can involve virtually any tissue but lungs are the most commonly affected organ.[1] Extra-thoracic sarcoidosis is present in one-third to half of patients, most commonly in the skin, peripheral lymph nodes, eyes, and liver.[1,31] The exact pathogenetic mechanism and cause of sarcoidosis are still unknown.[32] A postulated cause is an aberrant immunological reaction toward an as-yet-unknown antigen in a genetically susceptible individual.[32] The presence of non-caseating granulomas is the cardinal histological feature of sarcoidosis. These granulomas consist of tightly formed conjunctions of macrophages differentiating into epithelioid- and multinucleated giant cells, encircled by lymphocytes.[33] These need to be distinguished from caseating granulomas seen in tuberculosis and also from other granulomatous diseases.[34,35] According to a proposed immunopathogenic mechanism, a putative antigen is engulfed by circulating dendritic cells, which then mature in lymph nodes and present the antigen peptide to activate a T-cell response.[33] The ensuing response of the CD4+ T-cells is highly T-helper (TH) 1-polarized. This polarization is promoted and followed by a complex interplay and upregulation of a myriad of cytokines, including interleukin (IL) 2, IL12, interferon gamma, and tumor necrosis factor (TNF) alpha, released by both dendritic- and T-cells.[33]

The TH1 response is pro-inflammatory, while the TH2 response is characterized by a release of cytokines promoting immunoglobulin E and eosinophil activity. The TH2 response also releases anti-inflammatory cytokines, such as IL10.[36] The TH1 response is thought to trigger granuloma formation by recruiting macrophages and more lymphocytes to the inflammatory site. The inability of regulatory mechanisms to suppress the TH1 response might explain the uncontrolled formation of inflammatory granulomas in sarcoidosis patients.[37] Chronic granulomatous inflammation can lead to fibrosis. The specific immunological mechanisms of fibrosis generation are unknown but it is proposed that a switch from a TH1- to a TH2-dominant cytokine environment, such as IL13 and transforming growth factor beta, stimulates fibroblasts and myofibroblasts which are instrumental in the development of fibrosis.[33] To date, no specific sarcoidosis-causing antigen has been unequivocally identified, however. Table 1 lists common proposed triggers for the pathogenesis of sarcoidosis.

Table 1. Proposed infectious and non-infectious triggers associated with the pathogenesis of sarcoidosis

Infectious agents	Environmental factors
Mycobacteriae	Microbial bioaresols
Chlamydia pneumoniae	Silica
Cutibacterium acnes	Pesticides
Borrelia	Industrial organic dusts
Fungi	Metal dusts
	Combustible products
	Vitamin D deficiency

Two meta-analyses,[38,39] focusing on the link between infectious agents and sarcoidosis, suggested that mycobacteria[38,39] and Cutibacterium acnes[39] could be associated with sarcoidosis. Cutibacterium acnes (formerly Propionibacterium acnes), a commensal bacterium of the skin, is the only micro-organism that has been successfully isolated from sarcoid lesions.[40,41] Various non-infectious environmental risk factors have also been identified, such as exposure to both organic and non-organic aerosols.[42,43] For example, exposure to combustible products, such as in firefighters, has been associated with increased risk of sarcoidosis.[44] There seems to be a clear genetic susceptibility for the risk of developing sarcoidosis. A multicenter study showed that the relative risk of a sarcoidosis patient to report a parent or sibling with sarcoidosis was 4.7 (95% confidence interval (CI) 2.3–9.7).[45] A Danish-Finnish registry-based twin study demonstrated an 80-fold increased risk of sarcoidosis in monozygotic and a 7-fold increased risk in dizygotic co-twins of affected brothers or sisters.[46] Several candidate genes associated with sarcoidosis have been identified.[45,47,48] Autoimmune diseases including Sjogren's syndrome, systemic lupus erythematosus, thyroid and thymus disorders, inflammatory bowel disease, and insulin-dependent diabetes mellitus are reported in up to one fifth of sarcoidosis patients.[49–51, 52,53]

2.1.2 Giant cell myocarditis

The cause for GCM is unknown but as in sarcoidosis, a CD4+ T-cell process is suggested as the underlying pathogenetic mechanism.[54] It is possible that the etiology of GCM is multifactorial with microbial-, autoimmune-, and genetic causes all having a role.[55] One study found upregulation of multiple genes associated with T-cell mediated immune response, especially of the TH1 subset, in two GCM patients compared to six controls.[56] There are isolated reports associating GCM with an infectious microbial trigger. Suggested viral triggers include herpes simplex virus,[57] coxsackie B2 virus,[58] and parvovirus B19.[59] Vaideeswar et al. reported in a series of 12 GCM patients that three presented with an acute febrile

illness and two of them tested positive for leptospirosis.[60] Other autoimmune disorders are present in 19% of GCM,[3,6] supporting the hypothesis of an underlying autoimmune mechanism. Though considered a purely myocardial disease, GCM has anecdotally been described in concomitance with giant cell polymyositis and linked with thymoma, myasthenia gravis and orbital myositis.[61–66] Lastly, GCM has also been suggested as a manifestation of drug hypersensitivity.[67] Inflammatory bowel disease was the most common associated autoimmune disease in the landmark study by Cooper et al.[3]

Classical histological features of GCM include widespread myocardial necrosis with inflammatory infiltrate consisting of lymphocytes, histiocytes, eosinophils, and giant cells in varying proportions.[3,68] A histopathological study of eight GCM patients suggested a vasculitis-resembling process with inflammatory infiltrates encompassing small and medium-sized arteries leading to arterial stenosis and obliteration.[69]

2.2 Epidemiology

2.2.1 Sarcoidosis and cardiac sarcoidosis

The reported incidence and prevalence of sarcoidosis seem to be highest in Nordic countries.[70,71] In a register-based study from Sweden,[71] the incidence was 11.5 per 100 000. In contrast, in an epidemiological study from Japan, an incidence of only 1.01 per 100 000 was reported.[72] Ethnicity seems to play a role as the reported incidence and prevalence rates are consistently higher in African-American populations.[73,74] In one study from the US, the incidence per 100 000 was 46 in African Americans vs. 11 in Caucasians.[73] Arkema et al. reported that the prevalence of sarcoidosis in Sweden in 2013 was 160 per 100 000.[71] A report by Baughman et al.[74] estimated that the prevalence in the US was 60.18 per 100 000 in 2012. Table 2 demonstrates selected epidemiological figures in sarcoidosis. It should be noted that methodological pitfalls such as sampling bias and heterogeneity in diagnostic methods do complicate the estimation of reported incidence and prevalence data.[75,76]

Table 2. Selected epidemiological figures of sarcoidosis

Prevalence	49–160/100 000
Incidence	1–46/100 000
Ethnicity	More common in African Americans
Geography	More common in Nordic countries
Age	≈ 50 years, possibly a two-peaked incidence with first peak at ≈ 30 years and the second at ≈ 60
Sex	Slightly more common in women

Data is based on references[70–74,76,77]

Whether or not cardiac symptoms are present in the study population has a major impact on the reported epidemiological figures of CS.[78,79] CS can even manifest itself as SCD and these cases are typically not represented in epidemiological studies based on clinical registries. The reported detection rates of CS are also dependent on the diagnostic criteria used in each study (see also section 2.6.1). The most commonly applied sets of criteria have been the ones recommended by the Japanese Ministry of Health and Welfare (JMHW) and the Japanese Circulation Society (JCS),[80–82] the Heart Rhythm Society (HRS),[83] and the World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG).[84] The HRS and WASOG criteria are nearly identical but differ significantly from the JMHW/JCS criteria, which have also evolved over time.

The frequency of symptomatic CS in patients diagnosed with extra-cardiac sarcoidosis is often cited as approximately 5%,[83,85–87] with a variation from 1% to 16% between studies.[78,88–90] Asymptomatic cardiac involvement in sarcoidosis is much more common. In a study of 84 consecutive autopsied sarcoidosis patients, CS was present in 23 (27%) cases.[91] In another more recent study by Webb et al.,[92] CS was present in up to 38 (45%) of 84 consecutive autopsied decedents with sarcoidosis. Of note, African Americans comprised 95% of the study cohort.[92] It should be noted that CS is probably more likely present in fatal sarcoidosis cases; hence autopsy studies do present a selection bias.

Advanced cardiac imaging presents another way of evaluating the frequency of cardiac involvement (Table 3). Greulich et al.[93] reported that abnormal late gadolinium enhancement (LGE) was present in 39 of 155 (25.5%) consecutive sarcoidosis patients undergoing cardiac magnetic resonance imaging (CMRI). Kouranos et al.[94] reported on 321 sarcoidosis patients undergoing CMRI screening with CS diagnosed in 96/321 (30%) patients. LGE was present in 93 of these 96 patients. When an unselected population of systemic sarcoidosis is screened for CS, the yield is indeed dependent on the selected screening methods. For example, Darlington et al.[90] reported that 22 of 1017 (2%) consecutive sarcoidosis patients screened for CS by routine electrocardiography (ECG) and inquiries about cardiac symptoms were diagnosed with CS. Eleven of these 1017 (1%) had cardiac

symptoms, and an additional 11 (1%) asymptomatic CS patients presented with an abnormal ECG.

Table 3. Prevalence of abnormal LGE on CMRI indicative of CS in patients with systemic sarcoidosis undergoing screening for CS.

Study	Number of patients	% of patients with abnormal LGE
Prospective studies evaluating LGE presence in unselected sarcoidosis populations		
Cheong et al. 2009[95]	31	26%
Patel et al. 2009[96]	81	26%
Martusewicz-Boron et al. 2016[89]	201	24%
Kouranos et al. 2017[94]	321	29%
Puntmann et al. 2017[97]	53	34%
Stanton et al. 2017[98]	46	22%
Retrospective studies including sarcoidosis patients with suspected CS		
Smedema et al. 2005[78]	58	33%
Greulich et al. 2013[93]	155	26%
Crouser et al.2014[99]	50	45%
Nadel et al. 2015[100]	106	30%
Murtagh et al. 2016[28]	226	20%
Smedema et al. 2018[101]	84	32%
Flamee et al. 2020[102]	114	35%

CMRI indicates cardiac magnetic resonance imaging; CS, cardiac sarcoidosis; LGE, late gadolinium enhancement

Sarcoidosis confined to the myocardium, i.e., isolated CS, is a subset of CS where diagnostics can be especially challenging. The reported prevalence of isolated CS varies widely, being dependent on the studies performed to exclude extracardiac sarcoidosis.[4,9,103,104] Isolated CS can also present with SCD and escape clinical registries.[105] Routine clinical examinations, chest X-rays and laboratory tests may fail to detect extracardiac involvement in 57% to 67% of cases.[4,9] In these patients with clinically isolated CS, advanced imaging with CMRI, chest-computed tomography (CT), or ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) often expose extracardiac involvement. A report from our group (also based on the MIDFIN registry) concluded that 32% of 57 CS patients had sarcoidosis confined to myocardium even after assessment with ^{18}F-FDG PET during their early diagnostics.[103] In contrast, a prospective study from Canada, also utilizing ^{18}F-FDG PET, reported a notably smaller proportion of patients (3.2%) with isolated CS.[104] In an autopsy study, Tavora et al.[105] concluded that granulomas outside the heart could not be detected in 10 out of 25 (40%) victims of CS-related sudden death. The detection rates of CS are growing. In the US, the percentage of patients who had HF with CS requiring cardiac transplantation increased five-fold

from 0.1% (from 1994 to 1997) to 0.5% (from 2010 to 2014).[106] The advancements of cardiac imaging, in addition to improved awareness of CS, probably explain the growth in the detection rates of CS.[107]

In sarcoidosis, the average patient is in their fifties at the time of diagnosis.[71,72,88] A two-peaked incidence rate, especially in females, was reported in a Japanese population with the first peak at 25–34 years and the second at 60–64 years,[72] with very few patients younger than 20 or older than 80. Sarcoidosis is usually considered slightly more common in women[72,88] but contradictory data reporting male dominance also exists[71]. The age and sex distribution of CS do not differ from the demographics of sarcoidosis in general. In a Japanese study with 95 CS patients,[8] the mean age was 51±13 in patients diagnosed during their lifetime and 57±15 in patients diagnosed at autopsy with overall female predominance (65%). Females were also older at diagnosis than males (56±11 vs. 46±16; p=0.0004). In a nationwide series of 110 CS patients from Finland, the mean age of all patients was 51±9 with 65% of them being female.[9] These 110 patients were derived from the MIDFIN registry and are also a subgroup of the study population presented in this thesis. Studies reporting male predominance in CS also exist.[4,108]

2.2.2 Giant cell myocarditis

Earlier reports depict GCM as an extremely rare disease. GCM was first reported in 1905[109] and before the utilization of endomyocardial biopsy (EMB), the diagnosis was uniformly made at autopsy or after cardiac transplantation. The first reported case of improvement by immunosuppressive therapy was in 1987.[110] In the landmark study by Cooper et al.[3] in 1997, a total of 63 cases of GCM from 49 medical centers in 16 countries were identified. In one series of 4738 consecutive patients with EMB for clinically suspected myocarditis or dilated cardiomyopathy (DCM), GCM was diagnosed in 10 cases (0.2%).[111] Davies et al. reported that unexpected GCM was detected in 7 out of 340 consecutive (2%) explant studies after cardiac transplantation.[112] In a report of 174 consecutive patients with suspected myocarditis referred to a tertiary center for arrhythmias and cardiac transplantation over a 13-plus-year time period, GCM was diagnosed in five (3%) cases.[113]

Two reports from Finland include epidemiological data on GCM.[114,115]. Kytö et al. reported in 2005 that, after re-analysis, GCM was diagnosed in eight of 142 consecutive autopsy cases where the initial cause of death was recorded as myocarditis. These cases were detected from the national cause-of-death registry from 1970 through 1998.[114] In 2012 Kandolin et al. reported a series of 32 consecutive GCM patients in Finland.[6] The mean age was 49.5±11 at diagnosis in patients with a lifetime diagnosis from biopsy and there was a female (69%) predominance in the full cohort. In 2015, Kandolin updated the figures for GCM

describing 49 patients identified at Helsinki University Hospital between 1991 and 2014.[115] These patients[6,115] are also included in studies II and III of the present thesis. As described and detailed in the results of my work, all GCM cases of the MIDFIN registry were retrospectively re-evaluated in 2018, and a considerable part of the early GCM diagnoses was converted to CS (see results, section 5.1 and studies IIb, IIIb, IV, and V). Thus the previously reported figures[6,115] are not fully valid and must be interpreted cautiously. The mean age of patients in the landmark study of Cooper et al. in 1997 was 42.6±12.7 with a roughly equal number of men and women (33 vs. 30, respectively).[3]

2.3 Clinical manifestations in cardiac sarcoidosis

CS can be completely asymptomatic and might only be detected by cardiac imaging made either routinely or for ECG abnormalities in a patient with systemic sarcoidosis. The consequences of CS are determined by the location and extent of granulomatous infiltration and/or subsequent scarring in the heart.[14,105] The most commonly reported clinical manifestations of CS are AV conduction disturbances, VAs, and ventricular dysfunction. Typical symptoms therefore are syncopal episodes, palpitations, and dyspnea with exercise intolerance due to HF. However, the symptoms and clinical findings range from incidental ECG abnormalities[90] to even SCD as the first manifestation in a previously healthy person.[105] From a real-life clinical point of view, it should be noted that the various manifestations of CS typically overlap and co-exist in a single patient, e.g., AV block (AVB) with HF and/or VAs.[12]

2.3.1 Conduction disturbances

AV conduction defect is the most common evident clinical manifestation of CS. Reported rates of second degree or complete AVB in CS vary from 7% to 45%.[8,9,78,116] Sarcoid granulomas and subsequent scarring in the basal ventricular septum, where the AV conduction system is vulnerable, probably account for the majority of AVBs seen clinically.[14,105]

As patchy sarcoid infiltration can affect any part of the cardiac conduction system, many kinds of impaired impulse transmission can be seen, varying from complete AVB to intraventricular conduction defects.[117,118] AVB can also occur only during exercise.[119] Ischemia from granulomatous infiltration of the nodal artery is a less common cause of AVB.[120] CS should be suspected whenever an unexplained AVB in a relatively young patient is encountered.[121,122] In a study of 32 consecutive 18–60-year-old patients with an unexplained AVB, CS was subsequently diagnosed in 11 individuals (34%).[121]

2.3.2 Arrhythmias

VAs are common in CS and range from frequent premature ventricular extrasystoles to unexpected SCD due to VF. In a series of 15 consecutive patients with biopsy-proven thoracic sarcoidosis and no cardiac symptoms except palpitations in one patient, 24-hour ambulatory ECG recordings showed VAs in 4/15 (40%) patients including > 10 premature ventricular extrasystoles per hour in two patients, non-sustained VT in one patient, and sustained VT in one patient.[123] In a study of 38 sarcoidosis patients, of whom 12 had CS, > 100 premature ventricular extrasystoles per 24 hours were seen in 67% of CS patients compared to 8% of sarcoidosis patients with no cardiac involvement.[124] In 110 Finnish CS patients, sustained VT or VF was the first clinical manifestation of CS in one third of cases.[9] Nery et al. studied 14 patients with unexplained non-ischemic VT and found that CS was the underlying etiology in four (28%) cases.[125] In another study by Tung et al., CS was ultimately diagnosed in 18 (17%) of 103 consecutive patients referred for work-up of unexplained cardiomyopathy and VAs.[126] A recent study showed that CS was diagnosed in 4.5% of patients presenting with non-ischemic unexplained VAs.[127] SCD can be the first and only clinical manifestation of CS.[14,15,128] In an autopsy study from 1977,[14] SCD was the first sign of CS in 10 out of 89 (11%) cases. In another study from 1981,[15] Fleming and Bailey reported that out of 197 CS patients seen in a 10-year period, SCD was the first presenting manifestation in 34 (17%) cases. In contrast, another more recent autopsy study of 17 consecutive autopsied CS patients reported that all 11 patients with antemortem clinical data had symptoms prior to death but all escaped a lifetime diagnosis.[128] These symptoms varied from palpitations (4 out of 11) to HF combined with AVB (one out of 11).

Although atrial fibrillation (AF), atrial tachycardia and other supraventricular arrhythmias are commonly seen during follow-up of CS patients,[129] they are rarely the first sign of CS. None of the 110 consecutive CS patients reported by Kandolin et al.[9] had supraventricular arrhythmias as the main presenting manifestation. Weng et al.[130] reported that supraventricular arrhythmias were the predominating manifestation of CS in one out of 33 (3%) cases. On rare occasions, atrial CS can also manifest as sick sinus syndrome or even atrial standstill.[131,132]

Section 2.5 of this thesis reviews the mechanisms and characteristic of VAs in CS and GCM in more detail.

2.3.3 Heart failure

Ventricular failure in CS results from widespread myocardial inflammation and subsequent scarring. The presence of diastolic ventricular dysfunction is more common in pulmonary sarcoidosis patients than healthy controls and, although possibly of a multifactorial origin, it can be the first sign of cardiac involvement preceding systolic dysfunction.[133,134] HF with reduced ejection fraction is a sign of advanced CS and widespread involvement of the ventricles.[14] Besides resulting from direct myocardial destruction, HF can be a consequence of AV valve regurgitation from granulomatous infiltration of papillary muscles.[14] Focal inflammation can also lead to ventricular aneurysms (see Figure 1).[6,135] Although left ventricular (LV) or biventricular failure is the most common finding, CS can also cause isolated or predominant right ventricular (RV) failure mimicking arrhythmogenic right ventricular cardiomyopathy (ARVC).[136–140] Occasionally, RV failure can be a consequence of pulmonary hypertension that is caused by granulomatous infiltration of pulmonary vasculature, even in the absence of extensive pulmonary fibrosis.[141–143]

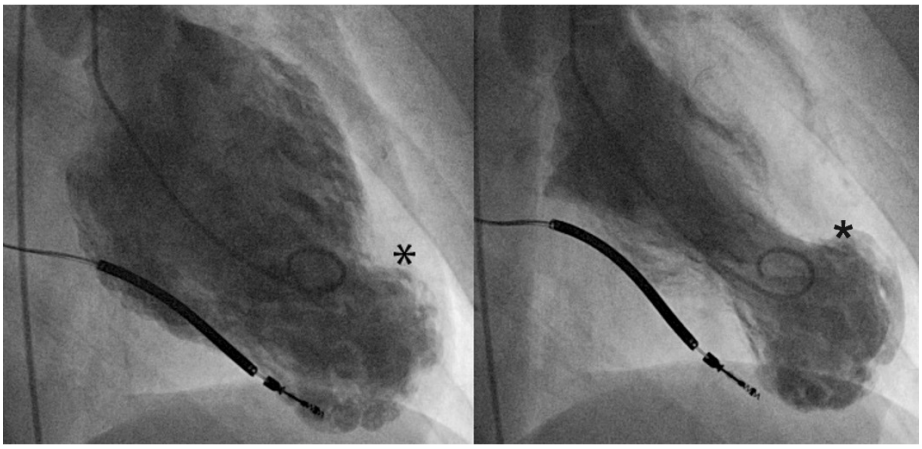

Figure 1. Ventricular aneurysm in cardiac sarcoidosis. A left ventriculogram in diastole (left panel) and systole (right panel) showing a large ventricular aneurysm (asterisk). Adapted from Kandolin et al. 2013[6]

In an early study from the UK,[15] HF was the predominant manifestation of CS in 17% of cases. Another study from 2001 reported that of 75 Japanese CS patients, as many as 36 (48%) had a depressed left ventricular ejection fraction (LVEF) (< 50%) at presentation.[8] In the modern era, with common utilization of advanced cardiac imaging and probably earlier detection of CS, congestive HF remains the predominant manifestation in 11–18% of cases.[9,144] CS can be misdiagnosed as idiopathic DCM or, less commonly, as hypertrophic cardiomyopathy.[140,145,146] A recent French nationwide study[140] reported that during a 17-year period, 15 CS patients were diagnosed from explanted hearts only after transplantation.

Twelve patients had a pre-transplantation diagnosis of DCM, two were diagnosed as hypertrophic cardiomyopathy and one as ARVC. It was concluded that in 77% of cases, CS could have been detected with non-invasive imaging techniques.[140]

During initial evaluation, concomitant AV conduction defects and regional ventricular wall thickness abnormalities are clues to suspecting sarcoid cardiomyopathy.[147] Also, mediastinal lymphadenopathy may serve as a sign of CS, although this can sometimes be seen due to mere congestive HF in DCM.[146]

2.3.4 Syndromes mimicking coronary artery disease

Chest pain associated with myocardial ischemia on thallium-201 scintigraphy without coronary artery obstructions has been reported in sarcoidosis.[148] Also, case reports of CS presenting as a syndrome mimicking myocardial infarction[149,150,151] or even takotsubo cardiomyopathy[152] exist. Sarcoidosis can affect coronary circulation in various ways. Sarcoid granulomas have been demonstrated to directly affect epicardial coronary arteries,[150,153] and impairment of hyperemic coronary circulation in areas of inflammation has also been described.[154] The improvement of myocardial hyperemic blood flow in inflamed areas after immunosuppressive therapy suggests a direct adverse effect of myocardial inflammation on coronary vasodilator capacity.[154] There are also reports of spontaneous coronary artery dissection in CS.[151,155,156]

2.3.5 Pericardial and valvular abnormalities

Pericardial effusion can be detected in up to 13–19% of CS patients,[116,157] but CS rarely presents mainly as a pericardial disease.[158–160] The most commonly seen valvular abnormality is mitral insufficiency,[161–164] but lesions of aortic[165] and tricuspid valve[166] have also been reported. Mitral insufficiency in CS is probably most often due to ventricular dilatation or direct sarcoid involvement of the papillary muscles.[14,162–164] In the early autopsy studies, papillary muscle involvement was present in 13–27% of cases.[14,91] Mild mitral insufficiency is not uncommon but severe cases with a fatal outcome[163] or which necessitate valvular replacement[162] have also been reported.

2.4 Clinical manifestations in giant cell myocarditis

Figure 2 demonstrates the differences and similarities of clinical characteristics in CS and GCM. The spectrum of clinical manifestations in GCM closely resembles the signs and symptoms of CS. There are, however, some differences in the distribution of the main disease manifestations.[4,7] Systolic LV impairment due to aggressive

inflammation and myocardial destruction is typical of GCM,[3,4,6,7,13] while AVB is the most common first sign of CS.[4,7,9] Sometimes diastolic LV dysfunction, probably caused by LV edema, can be the predominant mechanism of HF in the early course of GCM.[167] In the landmark multicenter GCM registry study, the main presenting manifestations were HF in 75%, VAs in 14%, a syndrome mimicking myocardial infarction in 6%, and AVB in 5% of all cases, respectively.[3] In 2003, after the inclusion of additional cases in the registry, it was reported that the majority (64%) of the 73 patients presented with a left sided HF; VT or VF was the main manifestation in 32%, and AVB in 15% of cases, respectively.[4]

In 2015, Maleszewski et al. reported on 26 selected GCM patients who had survived for more than one year without transplantation.[13] HF was the presenting symptom in 15 cases (58%). Recently, Nordenswan et al.[7] compared the characteristics of 351 CS patients and 28 GCM patients also derived from the MIDFIN registry. HF was the presenting manifestation in 50% of GCM vs. 15% of CS, while high-grade AVB was the first disease sign in 21% of GCM vs. 43% of CS.[7] Also, impaired LVEF (≤ 50%) was found at presentation in 81% in GCM vs. in 48% in CS. There are other less commonly reported symptoms and findings associated with GCM presentation. Vaideeswar et al.[60] reported that three out of 12 patients from an Indian population presented with an acute febrile illness. Larsen et al.[168] reported six cases of isolated atrial GCM. Four of these patients had AF as the main manifestation leading to diagnosis, one had HF and one had SCD.

The time from symptom onset to presentation at hospital and/or diagnosis is typically shorter in GCM than in CS. The reported median time from symptom onset to presentation was three weeks in the study by Cooper et al.[3] GCM typically has a much more aggressive clinical course than CS. However, GCM can have a protracted disease course,[13,169] while CS can present as fulminant myocarditis with rapid deterioration.[170–172]

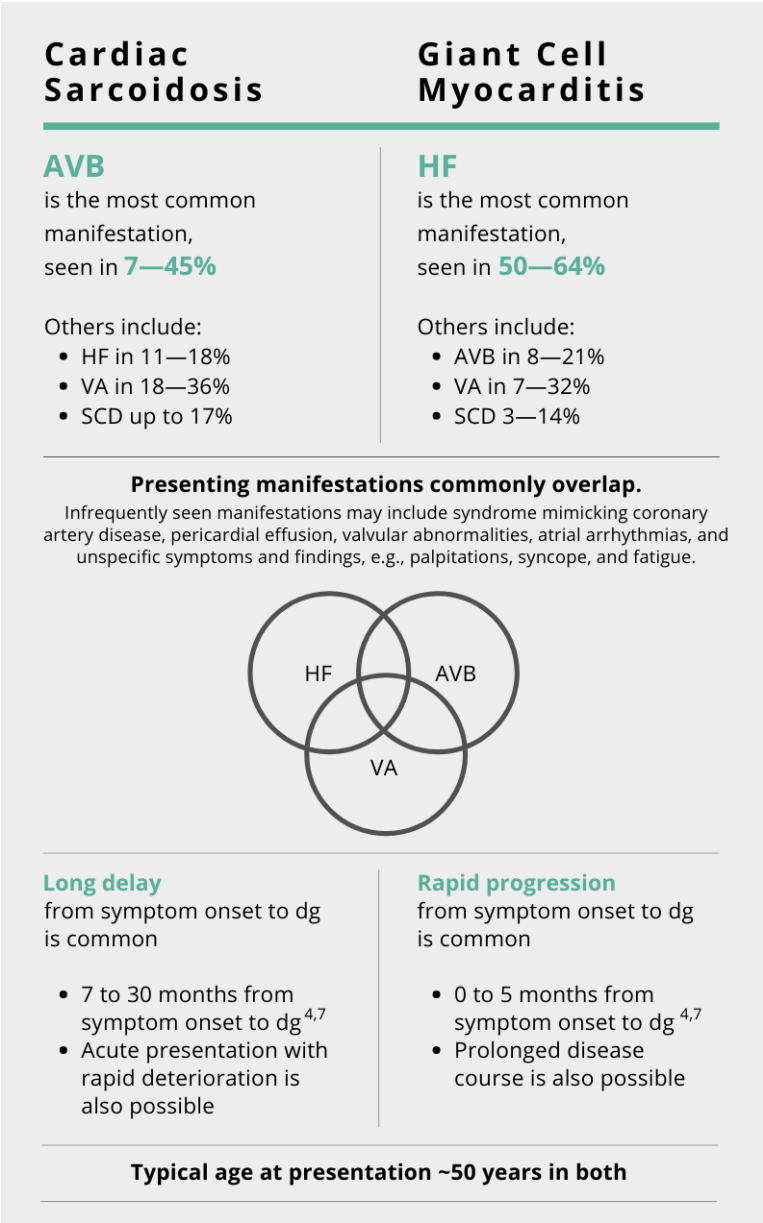

Figure 2. Comparison of clinical characteristics in cardiac sarcoidosis and giant cell myocarditis. Data from references[3–5,7–9,14,15,78,129,144]

AVB indicates atrioventricular block; HF: heart failure; SCD: sudden cardiac death; VA: ventricular arrhythmia

2.5 Pathogenesis, mechanisms, and characteristics of ventricular arrhythmias in cardiac sarcoidosis and giant cell myocarditis

2.5.1 Cardiac sarcoidosis

The majority of sustained monomorphic VAs seen in CS are scar-related monomorphic VTs caused by non-uniform and slow impulse propagation in scarred myocardium, leading to re-entry circuits.[18,19,22] Patterns of myocardial scarring in CS have been depicted across studies by gross anatomy,[105,14,91] imaging,[173–175] and/or electroanatomical mapping.[174–177] Virtually any part of the right, left, or both ventricles can be affected. Isolated RV involvement, however, is rare with only 2/25 cases reported in one autopsy study.[105] In the LV, scarring tends to be patchy with a predilection for the septum, anterior wall, and perivalvular regions.[174,176] In the RV, scarring detected by electroanatomical mapping is characterized by confluent regions of endo- and epicardium, with no predilection for any particular RV region.[176] Somewhat contradictory to this, Jefic et al. suggested a predilection for basal RV involvement resulting in peritricuspid re-entry.[177]

A preferentially mid-wall or epicardial scarring pattern was found in one CMR study, although one third of patients also had subendocardial LGE involving at least one LV segment.[173] The predilection for scarring of the epicardium is reflected by the frequent need for an epicardial RFCA to successfully abolish VTs.[176–179] Muser et al. described the characteristics of electroanatomical substrate in 42 CS patients undergoing high-density electroanatomical mapping and radiofrequency catheter ablation (RFCA), and compared these findings with CMRI and ^{18}F-FDG PET results.[174] They reported a predominance of abnormal substrate in the basal septum and perivalvular regions. They also showed that abnormal intracardiac electrograms (EGM) (generally considered potentially relevant targets for RFCA) were most likely to be found in areas with higher scar transmurality on CMRI. These areas also showed less evidence of active inflammation on ^{18}F-FDG PET. Multiple forms of monomorphic VTs in one patient are common and could be the result of heterogeneous and diffuse scarring, giving rise to multiple VT re-entry circuits. Typically, a median of three different forms of VT can be induced during programmed ventricular stimulation (PVS).[174–176]

While the contribution of myocardial necrosis and replacement fibrosis to arrhythmias in CS is well understood, the role of active inflammation is less clear. In lymphocytic myocarditis, polymorphic and irregular VAs were more commonly seen in the inflammatory phase.[180] These polymorphic VAs are the result of various mechanisms ultimately leading to automaticity and triggered activity.[181] Although similar data for CS does not exist, it can be speculated that pathophysiological mechanisms directly related to inflammation might be responsible for the

polymorphic VAs encountered in CS patients as well. In a study of 118 CS patients, inflammation detected by ^{18}F-FDG uptake with concomitant perfusion defects identified patients at higher risk of VAs.[182] Contradictory to this, Banba et al. could not demonstrate a correlation between inflammatory activity (detected by Gallium-67 scintigraphy) and new onset VTs.[183] Also, in CS patients undergoing electroanatomical mapping, abnormal EGMs are more likely to be found in scarred myocardium than areas with active inflammation.[174] This indirectly suggests that scar, rather than inflammation, might be the main driver for arrhythmias. It should be noted that active inflammation and scar-formation often co-exist and re-entry circuits can also be formed during ongoing active inflammation and granuloma formation (the inflammation-fibrosis continuum).[22,174] Re-entry is the most probable underlying arrhythmia mechanism, even in CS patients with active myocardial inflammation,[22] but whether the causative slowing of conduction is mainly due to areas of scarring or inflammation remains unclear. Lastly, inflammation-induced ventricular ectopy can act as a trigger for scar-related re-entrant VTs.[23] A rarer mechanism of VAs in CS could be related to inflammation-induced myocardial ischemia.[150,153,154,184] VT related to the Purkinje system has also been described with a narrower QRS duration than in scar-related VTs.[18]

2.5.2 Giant cell myocarditis

Compared to CS, less data on the mechanisms of VAs in GCM exists but given their histopathological and clinical similarities, it can be assumed that the electrophysiological phenomena underlying arrhythmias could be alike. Myocardial necrosis and the resulting replacement fibrosis are in general more extensive in GCM, giving rise to several re-entrant circuits. Reports of GCM patients undergoing electrophysiological study and/or VT RFCA describe successful induction of VTs by PVS and successful activation mapping of the tachycardia circuits, both indicative of a re-entry mechanism.[20,21] Graner et al. reported that in nine GCM patients a median of three (range 1–6) different VT morphologies per patient were encountered.[21] There are some case studies reporting that immunosuppressive therapy reduced incessant arrhythmias in acute settings,[25,26,185] suggesting a pathophysiological mechanism linked to inflammation in these cases.

Plakoglobin and other desmosomal proteins are responsible for myocardial intercellular linking, and their abnormalities are a key component in the pathophysiology of ARVC, a highly arrhythmogenic hereditary cardiac disease.[186] Defects in these linking sites can lead to cell death and progressive fibro-fatty replacement with strands of surviving myocardium acting as the media for re-entrant arrhythmias.[186] A disruption and reduced expression of these proteins are seen in both GCM and CS.[187] This might explain the resemblance of clinical arrhythmias seen in CS and GCM to those in ARVC.

2.6 Diagnostics of cardiac sarcoidosis

2.6.1 Diagnostic criteria and screening of cardiac sarcoidosis

The definitive diagnosis of CS stems from verification of sarcoid histology in a myocardial sample obtained, for example, by EMB, during cardiac surgery or upon studying the native heart after transplantation or at autopsy. In 1993 JMHW published guidelines on the diagnosis of CS.[81] They proposed in addition to a "histological diagnosis group" a "clinical diagnosis group," where a set of abnormalities in ECG, imaging, and other cardiac parameters combined with sarcoid histology obtained from extra-cardiac tissue was required. In 2006 JMHW revised these guidelines.[82] A histological verification was no longer required for the "clinical" diagnosis of CS. These guidelines were widely adopted despite the evidence that the sensitivity of the criteria is too low.[188,189] In 2017 the JCS further revised the 2006 guidelines. The key alterations were, first, the inclusion of findings on either ^{18}F-FDG-PET or CMRI in the "major criteria" category, and second, the addition of criteria for isolated CS.[80] In 2014 HRS published an expert consensus statement on the diagnosis and management of VAs associated with CS.[83] They also propose two pathways for diagnosing CS—a "histological" diagnosis from myocardial biopsy or a "clinical" diagnosis where an extracardiac histological diagnosis of sarcoidosis is combined with clinical and/or imaging findings consistent with CS. Also in 2014, WASOG developed a new sarcoidosis organ assessment instrument where, based on the consensus of a panel of sarcoidosis experts, criteria for cardiac involvement in the absence of myocardial histology were set.[84] According to the instrument, an extracardiac histological confirmation of sarcoidosis is necessary and then, based on different clinical and imaging findings including LGE-CMRI and ^{18}F-FDG PET if available, the diagnosis of CS is defined as probable (50–89% likelihood) or possible (< 50% likelihood). Table 4 summarizes the current diagnostic criteria of CS proposed by HRS, JCS, and WASOG.

Table 4. Diagnostic criteria for CS according to the HRS expert consensus statement, JCS guidelines, and the WASOG sarcoidosis organ assessment instrument

	HRS 2014*	JCS 2017†	WASOG‡
Definite CS	Positive myocardial biopsy	Positive myocardial biopsy	-
Clinical diagnosis group	Histological diagnosis of extra-CS and one or more of the following: • Cardiomyopathy or AVB responsive to immunosuppressive therapy • LVEF < 40% • Unexplained sustained (spontaneous or induced) VT • High-degree AVB§ • Abnormal ^{18}F-FDG uptake • Abnormal LGE on CMRI • Positive gallium uptake and other causes for the cardiac manifestation(s) reasonably excluded	Presence of extra-CS histology or clinical findings suggestive of pulmonary or ophthalmic sarcoidosis and 1. Two or more of the five major criteria 2. One of the five major criteria and two or more of the three minor criteria. Major criteria: • High-degree AVB§ or fatal VA • Basal thinning of the ventricular septum or abnormal ventricular wall anatomy • LVEF < 50% or focal ventricular wall asynergy • Abnormal gallium-67 scintigraphy or ^{18}F-FDG uptake on PET • Abnormal LGE uptake on CMRI Minor criteria: • Non-sustained VT, multifocal or frequent PVCs, BBB, axis deviation, or abnormal Q waves • Perfusion defects on SPECT • EMB: Monocyte infiltration and moderate or severe myocardial fibrosis	CS is probable (50–80%) if there is a histological diagnosis of extra-CS and one or more of the following: • Treatment responsive cardiomyopathy or AVB • Reduced LVEF in the absence of other clinical risk factors • Spontaneous or inducible sustained VT with no other risk factor • High-degree AVB§ • ^{18}F-FDG uptake on PET • LGE on CMRI • Positive gallium uptake • Defect on perfusion scintigraphy or SPECT scan • T2 prolongation on CMRI

* Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated With Cardiac Sarcoidosis [83]
† Japanese Circulation Society Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis[80]
‡ World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ Assessment Instrument[84]
§ Mobitz type II second-degree heart block or third-degree heart block

AVB indicates atrioventricular block; CMRI: cardiac magnetic resonance imaging; CS: cardiac sarcoidosis; EMB: endomyocardial biopsy; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; PVC: premature ventricular extrasystole; SPECT: single-photon emission computed tomography; VA: ventricular arrhythmia; VT: ventricular tachycardia; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography

Recommendations concerning screening patients with extracardiac sarcoidosis for cardiac involvement are available from the HRS and the American Thoracic Society.[83,190] The HRS statement recommends routine initial screening by ECG, echocardiography, and inquiry of cardiac symptoms.[83] The experts acknowledge, however, that the data backup is very limited; the recommendation was based only on two[79,191] small observational studies. In contrast to the HRS statement, the American Thoracic Society practice guidelines recommend only baseline ECG for sarcoidosis patients without cardiac symptoms or signs; these experts do not endorse routine echocardiography or 24-hour ECG recordings for screening purposes.[190] CMRI might be of significant additional value, as suggested by a 2017 study of 321 extracardiac sarcoidosis patients.[94] Using the HRS criteria as the standard for the presence of CS, CMRI was the most valuable screening tool with sensitivity and specificity of 96.9% and 100%, respectively.[94] In most institutions, however, issues with availability and cost-effectiveness prevent the wide-scale use of CMRI for routine screening. Mehta et al. compared the sensitivity and specificity of widely available diagnostic methods (query of cardiac symptoms, ECG, ambulatory ECG, and echocardiogram) against CMRI and ^{18}F-FDG PET suggestive of CS in 62 patients with extracardiac sarcoidosis.[79] An abnormal ambulatory ECG appeared to perform best with diagnostic sensitivity and specificity of 50% and 97%, respectively. If any of these baseline diagnostic tests were positive, the sensitivity and specificity were 100% and 87%, respectively.

Finally, the definitive diagnosis of isolated CS can be extremely difficult and requires a high index of suspicion and sometimes repeated biopsies. Sarcoid granulomas are typically focally present in the myocardium, significantly impairing the sensitivity of a single non-targeted EMB.[96,107,188,192] The latest Japanese guidelines allow a diagnosis of isolated CS without myocardial histology when a set of clinical and imaging findings is fulfilled.[80] This approach is susceptible to criticism, however, as there are no cardiac findings, either clinical, laboratory, or imaging-based, that are specific to CS.

2.6.2 Biomarkers

Angiotensin converting enzyme (ACE) levels are elevated in 60% of patients with sarcoidosis but lack specificity and sensitivity to be reliably used in the diagnosis or exclusion of sarcoidosis.[193] In suspected CS, elevated serum ACE activity, especially in combination with depressed LVEF, is linked to a higher likelihood of diagnostic EMB.[194] Elevated levels of high-sensitivity cardiac troponin I or T (hs-cTnT/I) indicate ongoing myocardial damage and can be useful markers of disease activity in CS.[195,196] Baba et al. showed that elevated hs-cTnT was indicative of active inflammation as judged by correlation with ^{18}F-FDG uptake on PET.[195] A study including 62 CS patients showed that hs-cTnT or hs-cTnI normalized in

67% of patients after initiation of immunosuppressive therapy.[196] Importantly, hs-cTnT/I was normal in 47% of patients at presentation, underlining the fact that normal troponin levels, even in untreated CS, are not uncommon.[196]

N-terminal pro b-type natriuretic peptide (NT-proBNP) is an unspecific indicator of myocardial wall stretch and neurohormonal activation.[197] Elevated NT-proBNP was accurate in identifying patients with cardiac involvement in a study of 150 Japanese sarcoidosis patients.[198] Concentrations of the soluble form of IL2 receptor have been shown to be elevated in serum and bronchoalveolar lavage of sarcoidosis patients.[199] Levels are elevated in patients with active sarcoidosis decreasing with therapy initiation, making soluble IL-2 receptor a potential marker of disease activity.[200] A multiple biomarker approach incorporating all the aforementioned biomarkers in diagnostics and risk stratification of sarcoidosis has also been reported.[201] The study concluded that NT-proBNP was useful in detecting cardiac involvement, ACE and soluble IL-2 receptor concentrations were higher in CS patients with concomitant extracardiac sarcoidosis and that hs-cTnI predicted fatal arrhythmias in CS.[201]

2.6.3 Echocardiography

Echocardiography is a useful first line imaging modality in suspected CS as it is non-invasive, widely available, and almost always performed during a cardiac outpatient visit. The HRS expert statement recommends echocardiography as a routine screening tool for CS in asymptomatic patients with extracardiac sarcoidosis.[83] In contrast, however, the more recent American Thoracic Society practice guideline advices against echocardiographic screening if cardiac symptoms and signs are absent and the ECG is normal.[190] Importantly, CS cannot be ruled out by echocardiography as findings can be normal in as many as 54–75% of confirmed CS.[79,202] The positive predictive value of an abnormal echocardiogram for CS in patients with extracardiac sarcoidosis was 83.9% in a study published in 2017.[94] Echocardiographic findings include LV dilatation, LV and RV systolic and diastolic dysfunction, regional wall-motion abnormalities not confined to a specific coronary artery territory, localized thinning or thickening of ventricular wall, especially of the basal septum, and ventricular aneurysms.[203,204] Although most findings are nonspecific for CS, thickness abnormality of the basal septum is considered more strongly suggestive of CS.[147,205,206] Ventricular septal thickening is probably related to granulomatous infiltration and edema in the acute phase whereas subsequent scarring is responsible for the abnormal thinning.[147,206] Figure 3 demonstrates thinning of the basal septum on echocardiography. Advanced echocardiographic methods, such as speckle tracking and strain imaging can be useful in early detection of subclinical cardiac involvement in sarcoidosis patients.[207,208] Echocardiography is an important follow-up tool in patients with

established CS as impaired LVEF, as well as impairment of initially normal LVEF, are predictors for adverse cardiac events.[27]

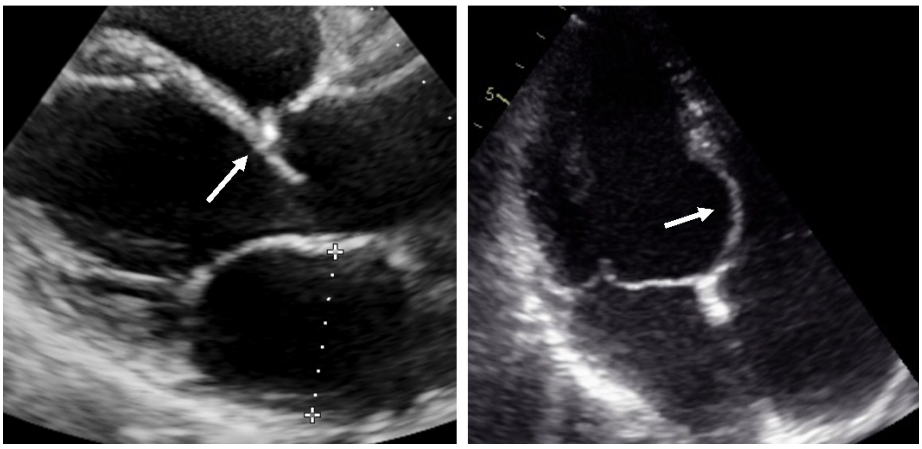

Figure 3. Thinning of the basal septum in cardiac sarcoidosis. Left panel: parasternal long-axis view showing abnormal thinning of the basal septum (white arrow). Right panel: Apical four-chamber view showing aneurysmatic thinning of the basal septum (white arrow).

2.6.4 Cardiac magnetic resonance imaging

Together with ^{18}F-FDG PET, CMRI is the imaging modality of choice in the workup of suspected CS.[83,209] Several different image acquisition protocols are used during a CMRI scan with each giving specific information. Cine-imaging is a very accurate method for delineating cardiac structure and ventricular function.[210] Quantitative measurements of ventricular volume, function and wall thickness can be made more accurately than with two-dimensional echocardiography. Structural and functional abnormalities are similar with those seen in echocardiography. In LGE imaging, the gadolinium chelate tracer distributes in the extracellular matrix of the myocardium in various patterns depending on the underlying pathological condition. Myocardial inflammation and myocyte destruction, as well as myocardial fibrosis due to collagen deposition, lead to an increase in the extracellular matrix and thus result in LGE.[211] No LGE pattern is pathognomonic for CS but typical findings include patchy LGE involvement, unrelated to coronary artery distribution, in basal and lateral segments and sometimes also in the RV (Figure 4).[96,202,212] LGE is especially common in the basal ventricular septum and is typically subepicardial or intramural, but can also be confined in the subendocardium or may even be transmural.[213] In T2-weighted CMRI, edema is detected by an abnormal ratio of signal intensity of suspected myocardium and skeletal muscle.[214] Quantitative T1 and T2 mapping has been proposed to increase

the accuracy of edema detection and to overcome technical pitfalls related to T2-weighted edema imaging.[97,215–217]

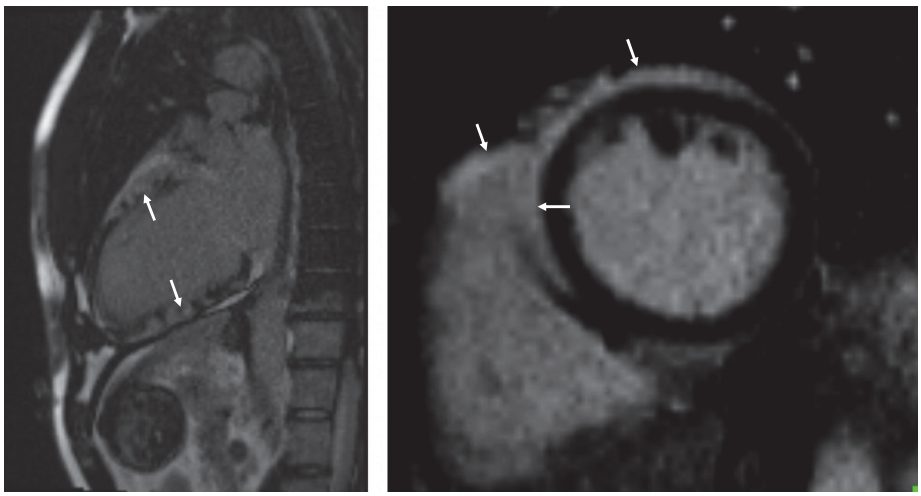

Figure 4. Cardiac magnetic resonance imaging showing abnormal late gadolinium enhancement (LGE). Left panel: long-axis slice where LGE is present in a widespread, patchy, mid-to-epicardial fashion (arrows). Right panel: short-axis slice showing confluent epicardial LGE extending into the interventricular junction and right ventricle (arrows).

The diagnostic performance of CMRI in detecting CS depends on whether JMHW/JCS,[80–82] HRS,[83] or WASOG[84] criteria are used as the reference. In a study of 321 patients with extra-cardiac biopsy proven sarcoidosis, and HRS expert consensus statement criteria as "gold standard", Kouranos et al.[94] calculated a sensitivity and a specificity of 97% and 100%, respectively, for CMRI in detecting CS. This translated to an area under the curve of 0.984 and positive and negative predictive values of 100% and 99%, respectively. Also, LGE was absent in only three (3%) of 96 patients with CS. In a meta-analysis of 649 patients, Zhang et al. compared the diagnostic efficacy of CMRI against the JMHW criteria and concluded an overall sensitivity and specificity of 94% and 85% respectively.[218] It is noteworthy that LGE on CMRI and ^{18}F-FDG uptake on PET are both listed as criteria for a clinical diagnosis of CS in the HRS consensus statement and as "major criteria" in the JMHW guidelines.[80,83] An important limitation of the above studies[94,218] is that the diagnostic performance of CMRI was tested against these sets of diagnostic criteria instead of the gold standard—myocardial histology. This explains the nearly perfect diagnostic performance of CMRI for the detection of CS in patients with proven extracardiac sarcoidosis in the study by Kouranos et al.[94]

CMRI can be useful when planning for VT RFCA as abnormal intracardiac electrograms are often seen in ventricular segments with LGE and these areas can be targeted for detailed electroanatomical mapping.[174,219] Finally, some reports

suggest that LGE could be used for monitoring treatment effect in CS[30,220] The prognostic role of CMRI is discussed separately in section 2.11.3.1

2.6.5 ^{18}F-fluorodeoxyglucose positron emission tomography

Inflammatory cells exhibit increased glucose metabolism, which can be imaged by utilization of ^{18}F-FDG, a glucose analog. Unlike glucose, ^{18}F-FDG is not metabolized further but stays in macrophages.[221] ^{18}F-FDG PET imaging is usually complemented with resting myocardial perfusion imaging to recognize areas of scarring and their relation to areas of inflammation.[221] A hallmark finding in CS is focal or multifocal ^{18}F-FDG uptake, suggesting active inflammatory activity, especially when seen in areas with abnormal perfusion (see Figure 5).[221–223] This type of mismatch pattern is, however, not always seen and some patients exhibit only multifocal abnormal ^{18}F-FDG uptake. Homogeneously increased ^{18}F-FDG uptake alone, especially in the lateral wall, is a nonspecific finding.[221,222] Scarring without ^{18}F-FDG uptake does not rule out CS as it can represent a "burned out" stage where no active inflammation is present.[223] Analysis of ^{18}F-FDG PET images has mainly been based on visual assessment, but quantitative techniques can also be used to measure the standard uptake value, which is the concentration of the radioactive tracer corrected by the injected dose and the patient's weight.[223,224]

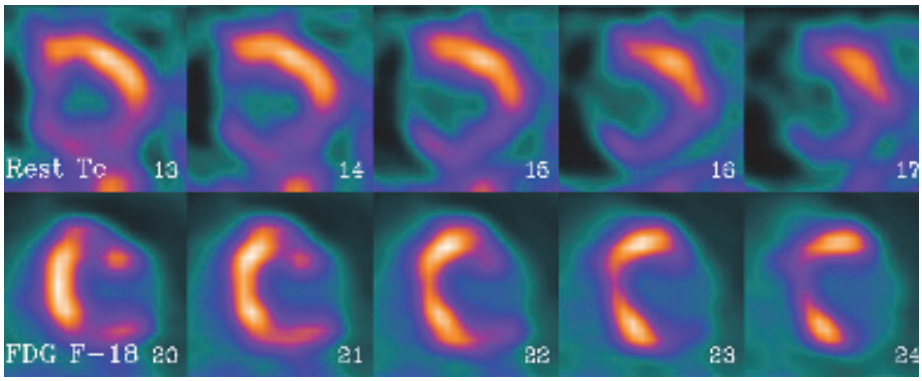

Figure 5. Perfusion-metabolism mismatch pattern. Short-axis ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (bottom row) and rest perfusion (top row) images from base (left) towards apex (right) showing a mismatch pattern typical of CS. Extensive myocardial uptake of ^{18}F-FDG is seen in an inferoseptal area, congruently with decreased rest perfusion.

CS patients very often have extracardiac sarcoidosis.[193] The diagnostic value of ^{18}F-FDG PET is increased by its ability to identify sites of extracardiac inflammation in the field of view of the scan, especially in the lungs and mediastinal lymph nodes (see Figure 6).[103,104,107] If EMB is undiagnostic but a strong suspicion for CS remains, "hot" mediastinal lymph nodes seen on ^{18}F-FDG PET should encourage a mediastinal lymph node biopsy to confirm the diagnosis.[107] A meta-analysis

from seven studies and 164 patients reported a pooled sensitivity of 89% and a pooled specificity of 78% of ^{18}F-FDG PET in detecting CS.[225] A more recent meta-analysis of 17 studies reported a pooled sensitivity of 84% and a pooled specificity of 83%.[226] A hybrid strategy combining the diagnostic value of both ^{18}F-FDG PET and CMRI has also been proposed and shown to increase the sensitivity and specificity of detecting CS.[227] A limitation of these studies is, however, the use of the JMHW diagnostic criteria as the reference standard, clouding the true diagnostic performance of ^{18}F-FDG PET.

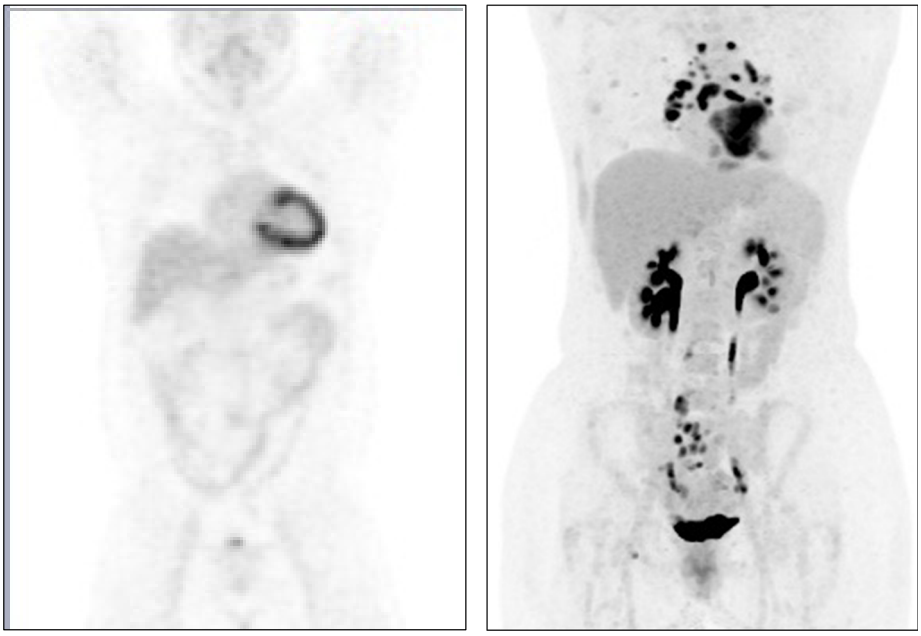

Figure 6. Whole-body ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography images. The left panel shows abnormal ^{18}F-FDG accumulation confined to myocardium (isolated cardiac sarcoidosis). The right panel shows both myocardial and mediastinal lymph-node ^{18}F-FDG accumulation.

Finally, ^{18}F-FDG PET imaging also gives quantitative information on the extent of inflammation and can thus be used to assess the disease severity and the treatment response.[223,228] Still, experts underline that it is unknown whether reduced ^{18}F-FDG uptake after immunosuppressive therapy is associated with reduced risk of major cardiovascular events.[223]

2.6.6 Endomyocardial and extracardiac biopsies

For a definitive diagnosis of CS, a myocardial sample demonstrating typical features of sarcoidosis must be obtained. Previous studies have reported that in suspected CS, non-targeted EMB results in a definitive diagnosis in only about 1 in 5 true cases.[96,107,188,192] This is explained by the patchy nature of the

inflammatory infiltrates in CS; if they are missed by the bioptome, CS remains undetected. The probability of a positive EMB is also higher in more extensive myocardial involvement. This was demonstrated by Uemura et al.,[188] showing that EMB resulted in diagnosis in 36.4% of cases presenting with a DCM-type disease compared to only 6.7% of cases presenting with conduction disturbances and a preserved LV function. Komoriyama et al. also showed that lower LVEF was associated with a higher probability of positive EMB.[194] Usually, the RV is primarily targeted for EMB[96,107,188,192] although, if indicated by imaging findings, LV biopsy can also be performed[107,229] with comparable complication rates to RV EMB.[230]

HRS recommends primarily pursuing a clinical diagnosis of CS by obtaining a biopsy from extra-cardiac sites, such as the mediastinal lymph nodes or lungs if they show evidence of disease activity; the reasoning being the relatively poor diagnostic yield of EMB and lower procedural risks of extracardiac biopsies.[83] Kandolin et al. reported that repeated EMBs eventually resulted in a definitive diagnosis in 55% of patients with high suspicion of CS.[107] The first EMB was diagnostic in 10 out of 31 (32%) patients but when EMB was repeated, in some cases up to three times, CS could be detected in seven additional patients. Importantly, the mediastinal lymph node biopsies exposed sarcoid granulomas per attempt much more often than EMB (11 out of 12; 92%). Finally, a small study has shown that, in suspected CS, a random biopsy of lungs or mediastinal lymph nodes may expose granulomatous inflammation even in the absence of any extracardiac ^{18}F-FDG uptake on PET.[231]

The previously reported figures[96,107,188,192] on the yield of non-targeted EMBs might not hold true in contemporary diagnostics of CS. Imaging by CMRI or ^{18}F-FDG PET can increase the diagnostic yield of EMB by revealing the most appropriate areas (e.g., RV vs. LV; basal vs. apical septum) to be targeted.[107,229] Higher rates of positive RV EMBs can be expected if there is evidence of RV and/or ventricular septal involvement on cardiac imaging.[96,182,232] Blankstein et al. reported that while the overall proportion of positive EMBs in 48 patients was 27%, it was 45% in the 20 patients with ^{18}F-FDG uptake on PET.[182] Moreover, of the six patients with RV ^{18}F-FDG uptake undergoing EMB, CS was detected in five (83%). Another study reported that 42% of patients with RV ^{18}F-FDG uptake had a positive EMB, compared to only 6% in patients without RV ^{18}F-FDG uptake ($p=0.024$).[232] In the study by Patel et al.,[96] 13 patients underwent EMB, of whom eight had LGE on CMRI. Two of the eight (25%) were diagnostic for CS. Of the 11 patients with negative EMBs, five had no LGE on CMRI and none of the remaining six had widespread septal involvement (two had no septal LGE at all). Komoriyama et al. showed that higher serum ACE activity was associated with a higher probability of a positive EMB.[194] When this was combined with low (< 37%, median) LVEF, the specificity and positive predictive value for positive EMB were as high as 91.2% and 73.7%, respectively. Electroanatomical mapping can also aid

in detecting areas relevant for EMB.[174,229,233,234] Muser et al. showed that abnormal unipolar voltage in areas with normal bipolar voltage correlated with the presence of active inflammation on ^{18}F-FDG PET, suggesting that these could be relevant targets for diagnostic biopsies.[174] Liang et al.[234] demonstrated that an abnormal EGM at the biopsy site predicted abnormal myocardium with a good sensitivity (67%) and specificity (92%), whereas normal EGMs with a voltage of > 5 mV signified normal myocardium with no significant diagnostic yield. Lassner et al.[111] proposed myocardial gene expression profiling to increase the diagnostic yield of EMB in suspected CS. Distinct gene expression profiles appeared to discriminate between patients with histopathological CS and GCM from inflammation-free subjects and from those with active myocarditis.

The principles and practice of CS diagnostics at Helsinki University Hospital have been detailed in several earlier reports.[9,12,107,235] In short, an absolute diagnosis from a sample of heart muscle has been the primary goal throughout these works. A diagnosis corresponding to the "probable CS" category by HRS[83] and WASOG[84] has been made in the presence of histological confirmation of extracardiac sarcoidosis combined with imaging and/or clinical findings of CS and the exclusion of other cardiac diseases. In contrast to the recommendation of the HRS statement,[83] EMB has been the preferred first biopsy procedure even in the presence of extracardiac involvement. Failing that, either an imaging-guided repeat EMB or extracardiac biopsy, depending on the details of the individual case, has been the next step. In selected cases of suspected serious isolated CS and negative EMBs, the diagnosis has been pursued by open-chest myocardial biopsy.[119,236,237] The flowchart in Figure 7 represents an overview of the diagnostic practice in our institution.

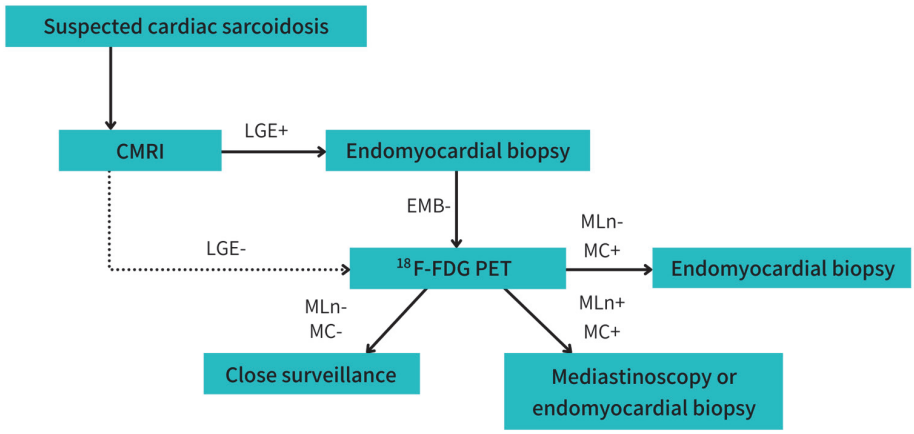

Figure 7. Diagnostic flowchart of suspected cardiac sarcoidosis at Helsinki University Hospital.

CMRI: cardiac magnetic resonance imaging; EMB indicates endomyocardial biopsy; LGE: late gadolinium enhancement; MC: myocardial; MLn: mediastinal lymph node; ^{18}F-FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography

2.7 Diagnostics of giant cell myocarditis

The diagnosis requires a myocardial sample showing histology compatible with GCM. Typically echocardiography shows a non-dilated LV with systolic dysfunction ranging from mild to extremely severe, depending on the stage of disease.[238–240] Other abnormalities seen include ventricular aneurysms and wall thickness abnormalities, especially local hypertrophy possibly due to inflammatory cell infiltrate and edema.[6,60,241,242] None of these findings are, however, specific or sensitive to GCM and rarely echocardiography can be normal or show only mild nonspecific findings at first presentation.[239,243] Data on CMRI in GCM is limited. Based on a few case reports, LGE can be seen in multiple myocardial areas and different myocardial layers in a non-coronary distribution.[243–246] In addition to widespread LGE, other CMRI findings include segmental hypokinesis, perfusion defects on first-pass perfusion imaging, high intensity signals representing edema on T2-weighted images, and diffusely impaired LV longitudinal strain.[245,246] In one case report,[245] areas of LGE on CMRI represented areas with GCM-specific histology at autopsy, while nonspecific inflammatory infiltrate was observed in areas exhibiting no LGE on CMRI. Published data on ^{18}F-FDG PET in GCM is even more limited. The resolution of ^{18}F-FDG PET uptake combined with clinical improvement can be seen in serial ^{18}F-FDG PET studies following successful immunosuppressive therapy.[247] Although cardiac biomarkers such as NT-proBNP and hs-cTnT/I levels are usually elevated in GCM, normal values at disease presentation are not absolutely exclusive of GCM.[6,7,248]

According to the American Heart Association (AHA)/American College of Cardiology (ACC)/European Society of Cardiology (ESC) scientific statement, to exclude GCM an EMB is indicated for patients with unexplained acute HF and hemodynamic compromise and for patients with refractory HF of subacute onset in the presence of LV dilatation, especially if one or more of the following are present: VAs, AVB, or failure to respond to usual care within one to two weeks.[249] As there is a wide variation in the clinical manifestations, and not all patients present with HF, a high index of suspicion is necessary.[3,6,60,238] Compared to CS, the diagnostic yield of EMB might be better in GCM with sensitivity up to 80–85% in cases with a fulminant disease course.[250]

The need for mechanical circulatory support is not uncommon in suspected GCM, and procuring myocardium for microscopy at ventricular assist device implantation is useful as larger and transmural samples can be studied.[4,6,250–253] Escher et al.[254] identified a distinctive gene expression profile specific for cases with a histologically verified GCM. Intriguing as this finding is, its interpretation and repeatability remain fully open.

2.8 Histopathological similarities and differential diagnostics of cardiac sarcoidosis and giant cell myocarditis

CS and GCM share many features in myocardial histology and their differentiation can sometimes be problematic, especially if sarcoidosis is confined to the myocardium.[4,35,111,255,256] Multinucleated giant cells are present in both CS and GCM.[4,35] Widespread, serpiginous myocardial necrosis associated with inflammatory cell infiltrates is typical for GCM,[3,4,35,68] whereas necrosis in CS is often less severe or absent (Figure 8),[4,35] although no specific threshold dividing GCM from CS exists. Okura et al.[4] reported that fibrosis was more commonly observed in CS than in GCM, although this finding could be biased by the timing of patient presentation. Fibrosis is a less common finding in the acute phase, compared to more advanced stages of the disease.[35] Eosinophils can be seen both in CS and GCM, although widespread eosinophilia is more common in GCM.[3,4,68] It is hypothesized that the cytotoxic substances of eosinophils could play a role in the typically extensive myocardial destruction of GCM.[4] Many experts think that the absence of myocardial granulomas in GCM is a key factor distinguishing it histologically from CS.[3,35,68] Differing views do, however, exist. In the landmark GCM study of 1997,[3] Cooper et al. underlined the absence of granulomas in GCM but, surprisingly, a later study by the very same group did not consider granulomas exclusive of GCM.[4] Cooper and Elamm have later specified that, in their view, poorly formed granulomas may be present in GCM but organized follicular granulomas containing central giant cells exclude this diagnosis.[257]

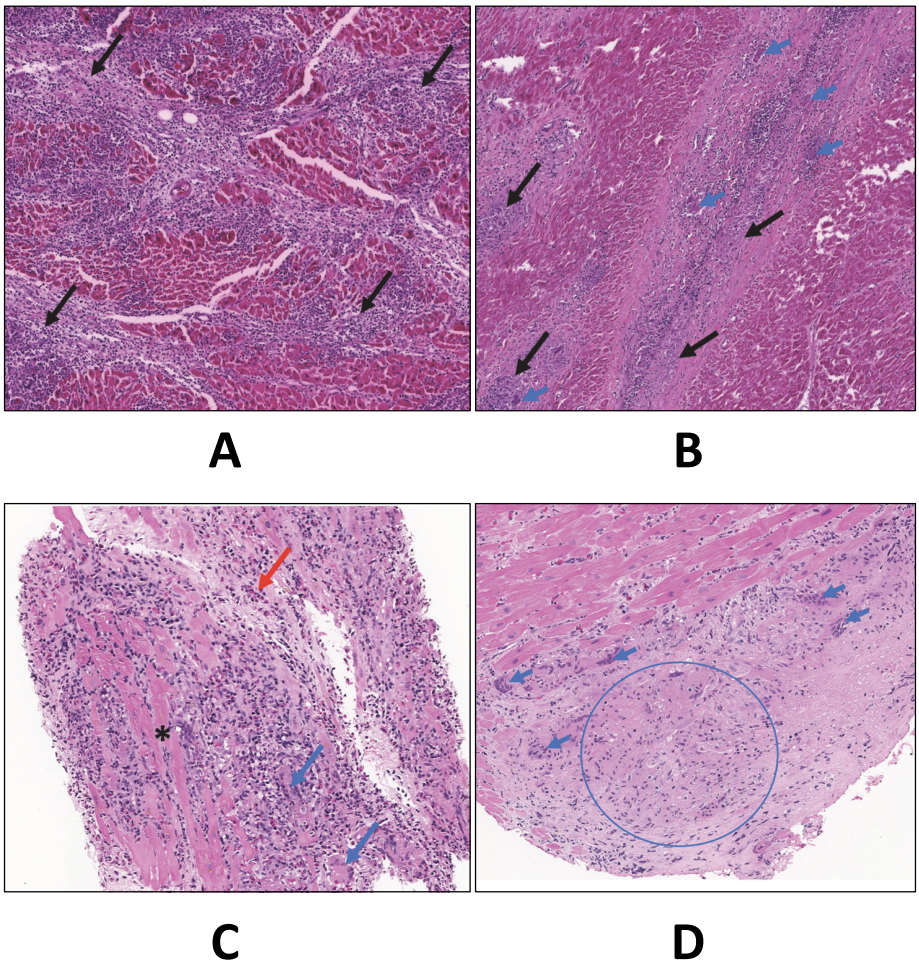

Figure 8. Histopathological characteristics of cardiac sarcoidosis (CS) and giant cell myocarditis (GCM)

Panel **A** demonstrates diffuse, serpiginous inflammatory infiltrate typical for GCM. In contrast panel **B** shows the well-demarcated inflammatory areas usually seen in CS. Black arrows point out the inflammatory infiltrates; epithelioid cell granulomas are also present at the foci identified by the black arrows in panel B. Panel **C** shows typical GCM histology with strands of surviving myocytes amongst diffuse myocardial damage (asterisk). Areas of abundant eosinophilia (red arrow) are also a hallmark of GCM. Panel **D** shows the granulomatous inflammatory infiltrates of CS. The blue arrows point out giant cells (in panels B-D) and the blue circle in panel D encompasses a large non-caseating epithelioid cell granuloma. The magnification coefficient was 100x (objective 10x, ocular tube 10x) in panels A and B and 200x (objective 20x, ocular tube 10x) in panels C and D.

In view of this, the differentiation between (definite) CS and GCM must be based on a full scrutiny of myocardial samples and needs to take into account all of the aforementioned histological characteristics (see Table 5). As GCM is considered a myocardial disease, the detection of granulomas outside the heart should favor the diagnosis of CS. The presence of extracardiac granulomas should be suspected, for example, when hot mediastinal lymph nodes on ^{18}F-FDG PET are present or findings consistent with pulmonary sarcoidosis are seen on CT. However,

several reports describing typical GCM histology on myocardial biopsy with proven extracardiac sarcoidosis exist,[68,258,259] further complicating the differential diagnosis. Lastly, myocardial gene expression profiling has been proposed to differentiate between GCM and CS.[111]

Table 5. Histopathological differences between GCM and CS

	GCM	CS
Granulomas	Absent*	Mandatory for diagnosis
Necrosis	+++	+
Giant cells	+++	+++
Eosinophils	++	+
Lymphocytes	++	+++
Fibrosis	+	+++
Pattern of inflammation	Diffuse inflammatory infiltrates	Sharply delineated inflammation

*Disagreement among experts whether the presence of granulomas is absolutely exclusive of GCM; see text (section 2.8) for details

+, ++, and +++ indicate the amount of a given feature on histopathological examination as mild, moderate, and severe, respectively

CS indicates cardiac sarcoidosis; GCM: giant cell myocarditis

2.9 Therapy

2.9.1 Background and general principles

The elements of the management of CS consist of immunosuppressive therapy, treatment of HF and VAs, and the prevention of SCD. Inhibition of inflammation by immunosuppressive therapy aims to preserve myocardial function. The drugs, devices, and interventional therapies used to treat HF and VAs in general[260–264] apply also for CS. Some CS-specific recommendations for the management of VAs and the prevention of SCD exist as well.[80,83,260,261] The risk stratification and prevention of SCD by implanting an implantable cardioverter defibrillator (ICD) constitute pivotal steps in the management of CS. A major problem is the total lack of prospective and controlled treatment trials. The practice of care therefore varies between institutions and is heavily dependent on local experience. The existing treatment recommendations[80,83,265] are based on the consensus of experts interpreting data from mainly small and retrospective observational studies.

2.9.2 Immunosuppressive therapy in cardiac sarcoidosis

Corticosteroids are the mainstay of immunosuppressive therapy in CS. The premise justifying corticosteroid use in sarcoidosis is based on the assumption that by inhibiting inflammatory granuloma formation and subsequent long-term fibrosis, organ function is preserved.[266] HF in CS is a result of widespread myocardial fibrosis,[14,91,267] but lesser degrees of fibrosis can still act as a substrate for life-threatening VAs.[22,174,176] The optimal dosage and duration of corticosteroid therapy in CS is still unclear. One retrospective trial showed no difference in survival between patients receiving initial high (≥40 mg) vs. low (< 30mg) dose prednisone.[8] Many authors suggest follow-up ^{18}F-FDG PET imaging for monitoring treatment response and tailoring immunosuppressive therapy.[24,86,223] Up until now there is, however, limited evidence to support that this improves treatment results. A prospective clinical trial is ongoing to address some of the unanswered issues of immunosuppressive therapy in CS.[268]

Typically, prednisolone is started at a dose of 20–60 mg daily and gradually tapered to a maintenance of 5 to 10 mg daily.[8,269–271] In a meta-analysis of 10 studies totaling 257 CS patients receiving corticosteroids, treatment duration varied from three to 168 months.[270] After discontinuation of corticosteroids, close follow up for relapses is recommended.[270] Some authors advise against stopping corticosteroids altogether,[272] while others suggest corticosteroid-sparing immunosuppressive therapy for long-term management.[273] In a retrospective single-center study from 2015, Nagai et al. found no benefit in terms of cardiac survival for 67 CS patients treated with corticosteroids vs. 16 patients not receiving corticosteroids for various reasons.[144] However, LVEF improved 7.9% and worsened 16.7% in patients receiving vs. not receiving steroids, respectively. Also, fewer HF hospitalizations were seen in patients receiving corticosteroid therapy. Data from retrospective small to medium-sized studies suggest that corticosteroid therapy might be associated with LV function maintenance or improvement in CS.[9,144,270,272,274] Sadek et al. outlined data on the association of corticosteroid therapy with LV function from four studies totaling 79 CS patients.[270] They concluded that corticosteroid therapy was associated with maintenance of normal LVEF or improvement in LVEF in patients with mild to moderate LV dysfunction, but no improvement was seen in patients with severely depressed LVEF at baseline. In 2016, Nagai et al. published a report comparing 49 CS patients receiving long-term corticosteroid therapy and 12 CS patients in whom steroid therapy was discontinued due to improvement of clinical condition.[272] Patients with discontinuation of prednisolone had a significantly greater percentage decrease in LVEF than those with continuation of therapy (% change in LVEF: −23.1 ± 11.9% vs +5.9 ± 5.4%, p = 0.037). Padala et al. reported that in a study of 30 CS patients, 14 had depressed LVEF at presentation, and that early initiation of corticosteroids in 9/14 patients resulted in an improvement of

mean LVEF (25% to 46%, P < 0.001) compared to no improvement in five of the 14 patients with delayed initiation of treatment.[274]

Evidence from small cohorts suggests that AV conduction can recover after initiation of corticosteroid therapy, especially when initiated early in the inflammatory phase.[272,274–276] Apart from prednisolone, no consensus exists on the use of other immunomodulatory drugs in CS. According a Delphi study in the United States,[277] most commonly used non-corticosteroid drugs were methotrexate, azathioprine, mycophenolate mofetil, and infliximab, an anti-TNF agent. Infliximab has been used as a second- or third-line drug for patients with persistent inflammation and/or side-effects from corticosteroid or other immunomodulatory drugs.[278–280] Based on small and retrospective case series, initiating infliximab may help reduce the dose of steroids with maintained or improved cardiac function, fewer VAs, and reduced inflammation on ^{18}F-FDG PET.[278–280] Side effects include thrombo-embolic, infectious, and allergic complications.[278–280] An earlier report suggested that infliximab may worsen HF in non-CS patients with depressed LVEF,[281] but this was not observed in the later reports focusing on infliximab use in CS.[278–280]

2.9.3 Immunosuppressive therapy in giant cell myocarditis

In their landmark study of GCM published in 1997, Cooper et al.[3] reported that in the 33 patients receiving immunosuppressive therapy, corticosteroids were used either alone or in various combinations with cyclosporine, azathioprine, and/or murine monoclonal T cell antibody (muromonab-CD3). The use of combination immunosuppression resulted in a better median survival compared to patients not receiving immunosuppression (12.3 months vs 3.0 months; p=0.001). Corticosteroids alone appeared not to improve survival. In 2008, a prospective randomized study was launched by the same group,[5] but only 11 patients could be recruited over a six-year period. All patients received a cyclosporine-based immunosuppressive therapy. Muromonab-CD3 was given to all but two patients. Corticosteroids were given intravenously for three days and then converted to oral prednisolone therapy. Without a placebo-arm, a benefit in terms of survival could not be concluded but serial EMBs revealed that after four weeks of treatment, the degree of necrosis, cellular inflammation, and giant cells decreased.[5] The scheme for immunosuppressive therapy in GCM in Helsinki University Hospital is described in detail in our earlier report.[6] In short, a triple combination of cyclosporine, prednisone, and azathioprine is the recommended treatment. Exceptionally, other immunosuppressive drugs, like mycophenolate mofetil, methotrexate, or the anti T-cell agent muromonab-CD3, have been added or substituted for the above agents. The target for maintenance cyclosporine concentrations has been in the lower range for immunosuppression after cardiac transplantation. It is

recommended to continue a small prednisone dose along with cyclosporine for prolonged periods.

There are some reports of encouraging results from the use of tacrolimus[282] and anti T-cell agents other than muromonab-CD3[25,283] in GCM. A recent expert consensus document on the management of acute myocarditis recommends anti T-cell agents together with high-dose intravenous steroids for fulminant GCM.[265]

2.9.4 Management of heart failure

Pharmacological therapy of heart failure with reduced ejection fraction in CS and GCM should be implemented according to the published guidelines on HF.[262–264] As in cardiomyopathies caused by other etiologies, ACE inhibitors and beta-blockers should be administered with the addition of a mineralocorticoid receptor antagonist to patients who remain symptomatic. In the 2016-published ESC and 2017-published ACC HF guidelines,[262,264] sacubitril/valsartan is recommended instead of ACE inhibitor for patients who remain symptomatic despite optimal ACE inhibitor, beta-blocker, and mineralocorticoid receptor antagonist therapy. In a 2021-published ACC expert consensus decision pathway for the optimization of HF treatment, direct initiation of sacubitril/valsartan is preferred to patients naive for ACE-inhibitors/angiotensin receptor blockers.[284] With limited disease-specific data, general recommendations regarding cardiac resynchronization therapy apply for GCM and CS.[262,263,285,286]

2.9.5 Transplantation in cardiac sarcoidosis and giant cell myocarditis

For eligible patients, cardiac transplantation is a worthy option for terminal HF or intractable recurrent VAs defying all other therapies. In CS, several studies report favorable long-term survival rates after cardiac transplantation. A retrospective analysis of transplantation outcomes from 38 US transplant centers spanning an 18-year time period reported a five-year overall survival of 80% in all 86 transplanted CS patients.[287] The authors observed a better one-year post-transplant survival in CS compared to other indications in a total of 38,165 contemporaneous patients.[287] Recurrence of CS in the allograft has been reported, sometimes even after several years post transplantation.[140,288]

In GCM, drug-and device therapy-resistant progressive HF and/or incessant VAs may necessitate cardiac transplantation. In their landmark study, Cooper et al.[3] reported that 34 of the 63 patients collected worldwide underwent cardiac transplantation. A report of 32 GCM patients from the United Network for Organ Sharing (UNOS) registry showed a post-transplant survival comparable to survival in DCM or other types of myocarditis despite higher rates of acute rejection in GCM.[289] Disease recurrence in the allograft is reported in 10–43% of cases of GCM,[3,6,112,290] and is often asymptomatic.[3,112]

In some cases, the use of mechanical circulatory support is necessary as a bridge to either recovery or transplantation. According to the UNOS registry, pre-transplantation support was necessary in more than half of GCM patients.[289] Another study concluded that of 41 GCM patients requiring mechanical circulatory support, 24 (58.5%) ultimately received cardiac transplantation.[253] In CS patients undergoing cardiac transplantation, mechanical circulatory support as a bridge to transplantation is necessary in a quarter of all patients.[291,292]

2.9.6 Management of ventricular arrhythmias

For the most part, the AHA/ACC/HRS and ESC general guidelines on management of VAs are applicable to patients with CS and GCM.[260,261] They also contain some CS- and GCM-specific recommendations. In addition, the JCS and HRS have published detailed recommendations for the management of VAs in CS.[80,87] The emergence of new data is reflected in the evolution of guidelines. For example, by giving more in-depth recommendations, the 2017-published AHA/ACC/HRS guidelines on the management of VAs superseded the 2008 ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities where it was briefly stated that ICD implantation is reasonable (IIa, level of evidence C) for patients with CS and GCM with no further specifications. The indications for ICD therapy in CS and GCM are discussed separately in section 2.13.

2.9.6.1 Anti-arrhythmic drugs and immunosuppressive pharmacotherapy

The role of immunosuppressive therapy in the treatment of VAs in CS is controversial.[144,177,270,272,293–296] Some studies report a reduction of VAs and a risk of cardiac death,[24,177,272,294,295] while others do not.[144] A study by Yogodawa et al. suggests that corticosteroid therapy could be beneficial in reducing VAs in the early stages of CS when LV function is still preserved.[294]

In another single-center study of 18 CS patients with VAs, a good antiarrhythmic response to immunosuppression and anti-arrhythmic drugs (AAD) was reported in patients with proven inflammatory activity on ^{18}F-FDG PET, while RFCA provided good results in patients without signs of active inflammation.[24] The 2014-published HRS expert consensus statement on the diagnosis and management of arrhythmias in CS, the 2017 JCS Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis and the 2017-published AHA/ACC/HRS guidelines for the management of patients with VA state that immunosuppressive medication can be useful in reducing VAs in CS.[80,83,260] It is however acknowledged that the data supporting this is limited.[83,260]

In GCM, incidental case studies have reported conflicting results of immunosuppressive therapy in reduction of VAs.[20,25,26,185,246,297,298] Resolution of inflammation by immunosuppression in the acute setting might prove successful in controlling the incessant VAs that are presumably associated with

inflammation,[25,26,185,298] whereas the monomorphic VTs seen later probably relate to myocardial scarring.[20,246]

There are no randomized trials on AADs in CS or GCM. In addition to beta-blockers, amiodarone is commonly used for the control of VAs in CS.[24,177] Class I AADs increase mortality in patients with previous myocardial infarction[299,300] and could have a similar adverse interaction with myocardial scarring due to CS or GCM as well. The HRS expert consensus statement advises against using class I AADs in CS.[83] In contrast, the JCS allows class I AADs for the management of uncontrollable VAs.[80] Incessant VAs can pose a major therapeutic challenge and impair the prognosis of patients with CS and GCM. In addition to AADs, augmentation of immunosuppression, or initiation of a combination immunosuppressive pharmacotherapy in newly diagnosed GCM, might be useful in controlling incessant VAs if there is evidence of ongoing inflammation.[23–26,83,298]

2.9.6.2 Radiofrequency catheter ablation of ventricular tachycardia

RFCA has been used for drug-refractory VAs in CS.[18,19,23,24,175–179,301–303] Several studies report encouraging results in VT suppression post-ablation, even though VT recurrences are common.[18,19,24,175–177,179] VAs are less frequent and more controllable by AADs post-ablation. In 2015, Kumar et al.[176] reported a one-year VT-free survival of only 37% after multiple RFCAs in 21 CS patients. Still, VT control was achieved in most of the patients with fewer AADs. In 2018 Papageorgiou et al. published a systematic review in which they identified 83 CS patients across five studies undergoing RFCA.[179] VT recurrence was observed in 54.2% of patients but 88.4% of patients were deemed to benefit from RFCA in terms of total freedom from VT or a reduction of VT burden. For GCM, data on RFCA is very limited and consists of solitary case reports.[20,26,297] It should probably be considered as a bail-out option but as the arrhythmic substrate is usually extensive, complete control of all VT circuits can be challenging.

The AHA/ACC/HRS or ESC guidelines for management of VAs do not give specific recommendations for RFCA in CS or GCM.[260,261] Some evidence exists that RFCA can control incessant VAs in both CS and GCM.[20,175,297] According to the HRS expert consensus statement, RFCA can be useful in CS patients suffering from incessant VAs and VAs refractory to immunosuppression and AADs.[83] Major complications include access site vascular complications, hemopericardium/cardiac tamponade and thromboembolic events.[304] In their systematic review, Papageorgiou et al. reported a complication rate of 4.7–6.3% in RFCA procedures in CS.[179] This is comparable to the reported complications rates of VT RFCA procedures in general.[304] In anecdotal cases, sympathetic denervation for VAs, unresponsive to AADs and RFCA, have shown favorable results.[305]

2.10 Long-term outcome

It should be noted that several factors complicate the interpretation of reported outcome data in CS and GCM. Survival figures depend on the analyzed outcome (e.g., overall survival, cardiac survival, transplant-free survival) and on whether the study included patients diagnosed only at autopsy. Study populations are usually relatively small, and composite endpoints are common. These endpoints typically consist, in addition to the "hard" endpoints mentioned above, of less severe events such as VT, development of AVB, or hospitalization for HF. As practically all prognostic studies are retrospective, some events may be less reliable than others and susceptible to subjective interpretation (e.g., hospitalization for HF). Also, in CS, the diagnostic criteria (JMHW/JCS guidelines,[80,82] HRS expert consensus statement,[83] WASOG criteria[84] or other institutional definition) vary between studies. In addition, some prognostic data has been derived from study populations comprising both confirmed and suspected cases of CS.

2.10.1 Overall and transplantation-free survival in cardiac sarcoidosis

Two retrospective studies from the early 21st century[4,8] and two more recent studies[9,108] report on overall- and transplant-free survival in CS. Yazaki et al.[8] studied 95 CS patients and reported an overall five-year survival of 75% in the 75 patients diagnosed during life and receiving corticosteroids. Okura et al.[4] studied and compared 42 CS patients (all with histological verification from myocardial biopsy) and 73 GCM patients and reported a five-year transplant-free survival of 60.5% in CS. In the 29 biopsy-diagnosed CS patients, survival was 69.8% at five years. Later, in 2015, Kandolin et al.[9] reported survival data from 110 consecutive CS patients in Finland (also a subgroup of the patient population presented in this thesis). The overall transplantation-free cardiac survival at five years was as high as 90% in all 110 patients. In the 102 patients diagnosed during life, the corresponding figure was 95%.[9] In 2017, Zhou et al.[108] reported that in 73 patients with probable or highly probable CS, transplant-free survival was as good as 96% at five years. Almost all (71 of 73 patients) received immunomodulatory treatment. Table 6 shows the one-, five-, and 10-year survival estimates in CS across studies.

Table 6. Studies reporting overall and transplantation-free survival in CS

Study	Number of patients (criteria for CS)	Outcome	1-year survival	5-year survival	10-year survival	Comments
Fleming et al. 1986[161]	250 (histological or clinical findings compatible with CS)	Overall survival	-	40%	-	
Yazaki et al. 2001[8]	95 (JMHW 1993[81])	Overall survival	85%	60%	-	Five-year survival was 75% in the 75 steroid-treated patients
Okura et al. 2003[4]	42 (histological verification from myocardium in all)	Transplantation-free survival	-	60.5%	-	Altogether, 74% received steroids and 24% received an ICD
Chiu et al. 2004[271]	43 (JMHW 1993[81])	Overall survival	98%	90%	84%	All patients received steroids. Only three patients received an ICD
Kandolin et al. 2015*[9]	110 (HRS[83])	Transplantation-free survival	99.1%	93.5%	89.3%	102 of 110 received immunosuppressive therapy and 54% received an ICD
Zhou et al. 2017[108]	73 (WASOG[84])	Transplantation-free survival	-	95.5%	93.4%	71 of 73 patients received immunosuppressive therapy and 59% received an ICD

*Also based on the MIDFIN registry

CS indicates cardiac sarcoidosis; HRS: Heart Rhythm Society; ICD: implantable cardioverter defibrillator; JMHW: Japanese Ministry of Health and Welfare; WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders Sarcoidosis Organ Assessment Instrument

2.10.2 Transplantation-free survival in giant cell myocarditis

In their study of 63 GCM patients by Cooper et al.,[3] the median transplant-free survival was only 5.5 months from symptom onset. However, as many as 25 (40%) of patients were diagnosed only at autopsy or from explanted hearts, likely biasing the overall survival figures. The median transplant-free survival for patients receiving immunosuppressive therapy was 12.6 months. The expanded GCM series of the same group[4] showed a transplant-free survival of only 10% at five years in 73 GCM patients, which differed markedly from the outcome in CS (see above). Of note, an ICD was implanted in only 12% and 24% of GCM and CS patients, respectively. In 2015 Maleszewski et al.[13] reported on 26 GCM patients surviving without transplantation for more than one year post-diagnosis. All patients received immunosuppressive therapy and an ICD was implanted in 65% of patients. The transplant-free survival at five years was 72%. Although better survival might be explained by advances in HF therapy and a higher rate of ICD implantations, a major survivorship bias is more than likely as patients dying within the first year of their diagnosis were excluded from the study. Table 7 shows studies reporting outcome in GCM.

Table 7. Studies reporting transplantation-free survival in GCM

Study	Number of patients	1-year survival	5-year survival	Comments
Okura et al. 2003[4]	73	-	10%	Five-year transplant-free survival was 21.9% in patients diagnosed from EMB
Cooper et al. 2008[5]	11	73%	-	All patients received cyclosporine-based combined immunosuppressive therapy
Maleszewski et al. 2015[13]	26	-	72%	Study limited to GCM patients surviving > one year after diagnosis

EMB indicates endomyocardial biopsy; GCM, giant cell myocarditis

2.10.3 Incidence of sudden cardiac death and life-threatening ventricular arrhythmias

2.10.3.1 Cardiac sarcoidosis

The occurrence of life-threatening arrhythmic events in CS patients is not uncommon in clinical practice. However, the true frequency of SCD due to CS is unknown, partly because CS may be completely silent until arrhythmic death, and these patients remain outside clinical CS registries. On the other hand, there is an unknown number of individuals with undiagnosed CS, surviving arrhythmia-free in the population, also complicating the estimation of the true risk of VAs.

Kandolin et al. reported that during a median follow-up of 6.6 years, only one of 110 CS patients died from HF, while 10 patients suffered an SCD and another 11 were successfully resuscitated from cardiac arrest.[9] Another study from Finland comprising 143 consecutive CS patients with high-degree AVB (also a subgroup of this thesis) concluded that the estimated five-year incidence of SCD was 17% and the five-year estimated incidence of either SCD or VT was 31%.[12] In a Japanese single-center study of 53 consecutive CS patients,[11] a total of 21 patients (40%) had a VF or VT during a median follow-up of 34 months. Table 8 lists more studies reporting the frequency of life-threatening VAs in CS. Finally, the risk of VAs may be especially high in the early course of CS. Segawa et al.[10] reported that 20 out of 68 (29%) CS patients had a VT after initiation of steroid therapy and that VT occurred within 12 months in 14 of the 20 patients.

Not surprisingly, appropriate ICD therapies are also common in CS (Table 9). Kron et al. reported on the outcomes of 235 CS patients with an ICD.[16,17] During a mean follow-up of 4.2 years, appropriate therapies (shocks or antitachycardia pacing) were seen in 85 of 234 (36%) patients and the annual therapy rate was 8.6%. Appropriate ICD therapy was seen in 33 of the 147 (22%) CS patients receiving an ICD for primary prevention.[17] A retrospective study from three centers in the US with 112 CS patients with an ICD reported that nearly a third received appropriate therapies during a mean follow-up of 29.2 months.[310] A VT storm (> three episodes in 24 hours) was seen in 16 (14.2%) patients. Of the 83 patients with a primary preventive ICD, 27.7% received appropriate therapies during follow up and the annualized event rate was also fairly high, at 11.3%. Appropriate ICD therapy is, however, not entirely synonymous with life-threatening VAs as many VAs treated by the ICD could still have been self-terminating.

Table 8. Reported incidences of life-threatening VAs in CS

Study	Patients	CS criteria	Follow-up	Outcome
Mehta et al. 2011[306]	76 consecutive CS patients undergoing PVS	HRS[83]	median 5.6 years	7% had appropriate ICD therapies or death from VA
Crawford et al. 2014[307]	51 CS patients with LVEF > 35%, undergoing CMRI	JMHW 1993 and 2006[81,82]	mean 2 years	25% had VT or VF
Ise et al. 2014[30]	43 CS patients undergoing CMRI	JMHW 1993[81,82]	mean 3.3 years	16% had life-threatening VAs
Kandolin et al. 2015*[9]	110 consecutive CS patients	HRS[83]	median 6.6 years	18% had SCD or aborted SCD
Takaya et al. 2015[11]	53 consecutive CS patients	JMHW 2006§	median 2.8 years	40% had sustained VT or VF
Segawa et al. 2016[10]	68 consecutive CS patients	JMHW 1993[81,82]	mean 5.5 years	29% had sustained VT or VF and/or appropriate ICD therapy
Muser et al. 2016[175]	31 CS patients undergoing VT RFCA	HRS[83]	median 2.5 years	52% had VT recurrence
Nordenswan et al.* 2018[12]	143 CS patients with high-degree† AVB	HRS[83]	median 2.8 years	The five-year incidence estimate of either SCD or VT was 31%
Chiba et al. 2020[27]	91 consecutive CS patients	JMHW 1993 and 2006[81,82]	mean 7.0 years	VT/VF-free survival estimate was > 80% in patients with LVEF ≥ 50% and < 20% in patients with LVEF < 50%
Gowani et al. 2020[308]	50 CS patients undergoing CMRI and ^{18}F-FDG PET	HRS[83]	mean 4.7 years	14% had sustained VT, VF, or appropriate ICD therapy
Manabe et al. 2020[309]	62 CS patients undergoing ^{18}F-FDG PET	JCS 2017[80]	median 3.1 years	6% had a sustained VT or VF
Rosenthal et al. 2020[29]	110 consecutive CS patients	HRS[83]	median 2.6 years	44.5% had SCD or sustained/symptomatic VT

*Both studies were based on the MIDFIN registry and include an overlapping patient population with the one presented in this thesis
†Mobitz II second- or third-degree AVB

AVB indicates atrioventricular block; CMRI: cardiac magnetic resonance imaging; CS: cardiac sarcoidosis; HRS: Heart Rhythm Society; ICD: implantable cardioverter defibrillator; JCS: Japanese Circulation Society; JMHW: Japanese Ministry of Health and Welfare; PVS: programmed ventricular stimulation; RFCA: radiofrequency catheter ablation; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography

Table 9. Studies reporting the frequency of appropriate ICD therapy in CS patients

Study	Number of patients	CS criteria	ICD for secondary prevention	Follow-up	Appropriate therapy
Aizer et al. 2005[311]	15	Suspected CS†	47%	Not reported for ICD receivers	60%
Mehta et al. 2011[306]	8	HRS[83]	0%	Median 5.6 years	50%
Schuller et al. 2012[310]	112	Modified JMHW‡	26%	Mean 2.4 years	32.1%
Betensky et al. 2012[312]	45	Author-modified§	35.6%	Mean 2.6 years	37.8%
Kron et al. 2013*[16]	235	Author-modified**	37.5%	Mean 4.2 years	36.2%
Mohsen et al. 2014[313]	30	Modified JMHW [82]	63.4%	Mean 3.75 years	36.6%
Takaya et al. 2017[314]	27	JMHW [82]	52%	Median 12 years	56%

*Includes 99 patients described earlier by Betensky et al. and Schuller et al.

†Tissue biopsy or Kveim test positive extra-CS and cardiac symptoms

‡ Additional criteria included LGE on CMRI and inducible VT on PVS

§ Extra-CS + fulfilled the JMHW criteria and/or had positive CMRI or ^{18}F-FDG PET or direct myocardial confirmation of sarcoidosis

**(i) biopsy-proven CS, (ii) CMRI findings suggestive of CS, or (iii) biopsy-proven sarcoidosis in another organ and presumptive cardiac involvement based on conduction system disease involving the sinus node, AV node, or His-Purkinje system and/or VAs.

AV indicates atrioventricular; CS: cardiac sarcoidosis; HRS: Heart Rhythm Society; ICD: implantable cardioverter defibrillator; JMHW: Japanese Ministry of Health and Welfare.

2.10.3.2 Giant cell myocarditis

Compared to CS, much less data exist on the incidence of VAs in GCM. The reports of the Multicenter GCM Study Group[3,4] showed that a ventricular tachyarrhythmia was the second most common presenting manifestation and developed in almost half of cases during the disease course. The study of one-year GCM survivors by Maleszewski et al. showed that six of 26 patients (23%) had VTs both at presentation and during a mean follow-up of 5.5 years.[13]

2.11 Prognostic factors in cardiac sarcoidosis

2.11.1 Clinical characteristics and biomarkers

Aside from one study reporting poorer outcomes in older patients,[108] age has not been associated with overall or transplant-free survival in CS.[4,8,9] The severity of HF symptoms (New York Heart Association functional class (NYHA)) predicted mortality in the study by Yazaki et al.[8] and transplant-free survival in the study by Kandolin et al.[9] Yazaki et al. also reported that sustained VT predicted worse overall survival.[8] Zhou et al. found that patients who received an ICD or pacemaker had a better transplant-free survival, but the authors speculated that the more favorable prognosis might have been related to a closer cardiac follow-up rather than to the device per se.[108]

Kron et al. reported that appropriate ICD therapies were associated, in addition to lower LVEF, with male sex, history of syncope, ventricular pacing at baseline ECG, and a secondary preventive indication for an ICD ($p< 0.05$ in all).[16] In a later study of the same population, the authors also concluded that patients with isolated CS had high rates of appropriate ICD therapies (69.2% vs 33.8% in patients with cardiac and extracardiac sarcoidosis; $p=0.015$).[17] Of note, isolated CS was also associated with a composite end-point of cardiac survival free of transplantation and aborted SCD in the report by Kandolin et al.[9] Two studies describe the arrhythmic risk of CS patients presenting with AVB.[11,12] Nordenswan et al. reported that the rate of SCD in CS patients with AVB and LVEF > 50% was 9% at five years,[12] and Takaya et al. reported that the rate of cardiac survival free of VF or VT was similar between CS patients with AVB and CS patients with previous VT and/or HF[11]. A recent meta-analysis[315] reported that in patients who had appropriate ICD therapy, high-degree AVB was more frequent ($p=0.05$). Interestingly, ICD indication (primary vs. secondary preventive), age, or LV function did not differ between the group who had appropriate ICD therapy vs. the rest.

Limited data on the prognostic role of cardiac biomarkers in CS exist.[196,201] Kiko et al.[201] reported on 49 CS patients and concluded that, in a multivariate model accounting for LVEF with 11 fatal arrhythmias as endpoint events, higher cTnI values at baseline were predictive of adverse outcomes with a hazard ratio (HR) of 2.348 (95%CI 1.272–4.333). In the work by Nordenswan et al.,[7] cTnT/I levels were independently associated with a composite endpoint of fatal or aborted cardiac death or transplantation after adjusting for CS vs. GCM diagnosis, LVEF, and BNP level. BNP levels were predictive of outcome in a univariate analysis but lost their significance when adjusted for the aforementioned parameters.

In summary, earlier VAs and a history of syncope predict increased risk of future life-threatening VAs in CS. Additional risk factors include presentation with AVB, isolated CS, higher NYHA functional class, and having either ventricular-

paced rhythm or high circulating concentrations of cardiac troponin or BNP at the onset of follow-up. The data regarding age and sex as risk factors is somewhat conflicting.

2.11.2 Ventricular function

Several studies have linked impaired LV function with worse overall and transplant-free survival in CS.[8,9,108] It has also been consistently associated with varying composite adverse endpoints including, in addition to mortality and transplantation, HF hospitalization, life-threatening VAs, and development of AVB.[27,30,316] Of note, ventricular aneurysms, present in 8–40% of CS cases,[14,135] are also linked to adverse cardiac events[135] and can usually be readily detected by echocardiography. Basal thinning of the interventricular septum in CS patients, not an uncommon morphological finding, has also been associated with future adverse cardiovascular events.[317] Severely reduced LV function (LVEF < 35%) is a well-recognized risk indicator for future life-threatening VAs in cardiomyopathies in general.[260,261] CS does not make an exception to this,[10,12,16,27,310] but perhaps due to concomitant active inflammation and progressive scarring, many patients with near-normal to normal LVEF may still be at significant risk of later VAs.[11,12,16,27,29,312,315] Table 10 lists studies reporting on the association of LVEF and life-threatening VAs in CS. In the study by Rosenthal et al.,[29] 49 of 110 CS patients (44.5%) had a VA or SCD over a median follow-up of 2.6 years. Importantly, a significant proportion (38.5%) of the 78 patients in the subgroup with LVEF ≥35% also had an arrhythmic endpoint. Also, after adjustment for age, presence of CAD or chronic kidney disease, LVEF of < 35% did not predict VAs or SCD.[29] In a recent meta-analysis on the role of ICDs in CS, no difference in LVEF was seen in patients having vs. not having appropriate ICD therapies.[315] Kron et al.[16] and Betensky et al.[312] have also shown that a major proportion of appropriate ICD therapies in CS occurs in patients with LVEF > 35%. Chiba et al. found a significantly better VT/VF-free survival in 56 CS patients with LVEF > 50% compared to 35 patients with LVEF < 50% but, still, seven (13%) out of the 56 patients with LVEF > 50% experienced a VT or a VF during a mean follow-up of 84 months.[27] Nordenswan et al.[12] reported that CS patients with AVB and prior VT or LVEF < 35% had a higher risk of fatal or life-threatening VAs than individuals with AVB and LVEF 35–50%. However, even in the subgroup of lone AVB comprising patients with LVEF> 50% and no history of VTs, the estimated five-year incidence estimate of SCD or VT was as high as 24%. Lastly, besides LVEF, RV ejection fraction (RVEF) has also been associated with adverse outcomes.[28,212,310] In conclusion, although depressed LVEF is a robust overall risk indicator in CS, many patients with near-normal to normal LV function still have a high risk of life-threatening VA.

Table 10. Studies evaluating the association of LVEF and risk of life-threatening VAs in CS

Study	Patients	CS criteria	Follow-up	Results
Kron et al. 2013[16]	235 CS patients with an ICD	Author-modified‡	4.2 years	The mean LVEF for patients who received appropriate ICD therapies was lower compared with those who did not (38.1 ± 15.2 vs. 48.8 ± 14.7, P < 0.0001).
Takaya et al. 2015[11]	22 CS patients with high-degree† AVB	JMHW 2006[82]	median 34 months	LVEF < 50% was not predictive of cardiac death, VT, or VF
Segawa et al. 2016[10]	68 CS patients	JMHW 1993[81]	mean 5.5 years	LVEF was a predictor for VT/VF (HR 0.94; 95%CI 0.90–0.97)
Nordenswan et al. 2018*[12]	143 CS patients with high-degree† AVB	HRS[83]	median 2.8 years	LVEF was associated with SCD or VT (SHR 1.39; 95%CI 1.03–1.86)
Chiba et al. 2020[27]	91 CS patients	JMHW 2006[82]	mean 84 months	VT/VF-free survival was better in patients with LVEF ≥ 50%
Rosenthal et al. 2020[29]	110 CS patients	HRS[83]	median 2.6 years	Patients with LVEF < 35% had greater occurrence of sustained VT/VF/SCD

*Based on the MIDFIN registry and represents an overlapping patient population with the one presented in this thesis

†Mobizt II second- or third-degree AVB

‡(i) biopsy-proven cardiac sarcoid, (ii) magnetic resonance imaging (MRI) findings suggestive of cardiac sarcoid, or (iii) biopsy-proven sarcoidosis in another organ and presumptive cardiac involvement based on conduction system disease involving the sinus node, AV node, or His-Purkinje system and/or ventricular arrhythmias.

AVB indicates atrioventricular block; CS: cardiac sarcoidosis; HR: hazard ratio; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; PM: pacemaker; SCD: sudden cardiac death; SHR: subdistribution hazard ratio; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia

Table 11. Studies evaluating the prognostic significance of CMRI in CS

Study	Patients	Follow-up	Main findings
Studies including only patients with a diagnosis of CS			
Shafee et al. 2012[316]	61 CS patients (according the JMHW 2006 criteria[82])	mean 45 months	The composite (cardiovascular death, NSVT, sustained VT, VF, or HF hospitalization) endpoint-free survival was worse in patients with LGE. LGE was not a predictor of life-threatening VAs
Crawford et al. 2014[307]	40 CS patients (according the JMHW 2006 criteria[82]) with LVEF > 35% and no prior VT/VF	mean 48 months	The PPV and NPV values of LGE presence for VT/VF during follow-up were 22% and 100%, respectively
Ise et al. 2014[30]	43 CS patients (according the JMHW 1993 criteria[81])	mean 39 months	LGE mass was an independent predictor of a composite of cardiac death, HF hospitalization, and life-threatening VAs. LGE was not a predictor of life-threatening VAs
Studies including mixed populations of patients with suspected CS, confirmed CS, and extra-CS with or without cardiac symptoms			
Patel et al. 2009*[96]	81 sarcoidosis patients screened for CS; 21% with cardiac symptoms	mean 21 months	Event rate of a composite of all-cause mortality, appropriated ICD therapy or bradycardia necessitating PM implantation was nine times higher in patients with LGE
Greulich et al. 2013[93]	155 patients with suspected CS	median 2.6 years	LGE was an independent predictor of a composite of death, aborted SCD or appropriate ICD therapy
Nagai et al. 2014[205]	61 patients with extra-CS without cardiac symptoms	mean 50 months	No difference in a composite of all-cause death, symptomatic arrhythmia or HF hospitalization between LGE+ and LGE- groups
Nadel et al. 2015[100]	106 patients with cardiac or extra-CS	mean 36.8 months	Presence of LGE compatible with CS was a strong predictor of a composite of SCD and VT
Murtagh et al. 2016[28]	226 patients with biopsy proved extra-CS. Majority did not have cardiac symptoms	mean 36 months	The presence of LGE, the percentage amount of LGE, RVESVi, and RVEF were significantly associated with a composite of death or VT.
Agoston-Coldea et al. 2016[318]	56 patients with extra-CS and suspected CS	mean 32 months	LGE extent was an independent predictor of a composite of death or aborted death from cardiac cause, VT, HF hospitalization, or development of AVB
Yasuda et al. 2016[319]	81 patients; 35 with CS according JMHW 2006 criteria[82] and 46 with suspected CS	median 22.1 months	A high LGE mass index was associated with VA-free survival and with a composite of cardiac mortality, HF hospitalization, AVB, and VA. An LGE localization score (high vs. low) was also predictive of the same study endpoints.
Kouranos et al. 2017[94]	321 sarcoidosis patients screened for CS; 50% with cardiac symptoms	median 84 months	LGE was an independent predictor of a composite of death, life-threatening VAs, HF hospitalization, and cardiac transplantation
Smedema et al. 2017[320]	84 patients with pulmonary sarcoidosis. Twenty-five had cardiac symptoms and 21 fulfilled HRS criteria[83] for CS	median 56 months	RV, LV, or biventricular LGE were predictive for a composite endpoint of HF hospitalization, sustained VA, appropriate ICD therapy, PM for AVB, or cardiac death. Biventricular LGE was the only independent predictor of outcome in multivariate analysis.
Kagioka et al. 2019[212]	103 patients; 48 with definitive CS according JCS criteria[80] and 55 with suspected CS	median 20.6 months	RVEF and RV LGE were independent predictors of a composite of cardiac mortality, VA, HF hospitalization, or development of AVB.

AVB indicates atrioventricular block; CMRI: cardiac magnetic resonance imaging; CS: cardiac sarcoidosis; HF: heart failure; HRS: Heart Rhythm Society; ICD: implantable cardioverter defibrillator; JMHW: Japanese Ministry of Health and Welfare; LGE: late gadolinium enhancement; NPV: negative predictive value; NSVT: non-sustained ventricular tachycardia; PM: pacemaker; PPV: positive predictive value; RVEF: right ventricular ejection fraction; RVESVi: right ventricular end-systolic volume index; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia

Table 12. Studies evaluating the prognostic significance of 18F-FDG PET in CS

Study	Patients	Follow-up	Findings
Studies with CS patients only			
Muser et al. 2016[175]	23 CS (HRS criteria[83]) patients undergoing RFCA for VT	Median 2.5 years	Abnormal ^{18}F-FDG uptake in 15/23 patients. A positive baseline ^{18}F-FDG PET and a lack of PET improvement predicted recurrence of VT
Muser et al. 2018[174]	20 CS (HRS criteria[83]) patients undergoing RFCA for VT, all with serial ^{18}F-FDG PET data	Median 35 months	Reduced ^{18}F-FDG uptake on serial PET predicted lower risk of MACE (death, transplantation, HF hospitalization, appropriate ICD therapy)
Gowani et al. 2020[308]	50 CS patients (HRS criteria[83]) and both CMRI and ^{18}F-FDG PET imaging	Mean 4.1 years	NPV of LGE and ^{18}F-FDG absence for VAs during follow-up were 100% and 79%, respectively. ^{18}F-FDG-PET imaging did not offer additional prognostic value in LGE-positive patients.
Manabe et al. 2020[309]	62 CS (JCS 2017 criteria[80]) patients	Median 3.1 years	Patients with high ^{18}F-FDG uptake heterogeneity in ^{18}F-FDG PET texture analysis had more MACE (all-cause death, sustained VT or VF, AVB or HF hospitalization)
Studies with mixed sarcoidosis and CS populations			
Blankstein et al. 2014[182]	118 patients with known or suspected CS. ^{18}F-FDG PET was abnormal in 31%	Median 1.5 years	Abnormal perfusion, ^{18}F-FDG uptake, perfusion together with ^{18}F-FDG uptake, and RV ^{18}F-FDG uptake were predictive of death or sustained VT
Sperry et al. 2017[321]	84 sarcoidosis patients; 58% and 83% positive for CS by JMHW 2006 [82] and HRS criteria[83], respectively	Median 17.5 months	Number of myocardial segments with abnormal ^{18}F-FDG uptake was predictive of MACE (all-cause death, transplantation, VT, or HF hospitalization)
Bravo et al. 2017[322]	56 patients with high suspicion of CS undergoing both ^{18}F-FDG PET and LGE CMRI	Median 2.6 years	In multivariate analysis, presence of LGE was the only independent predictor of death and/or malignant VAs.
Wicks et al. 2018[227]	51 patients with suspected CS undergoing simultaneous ^{18}F-FDG PET and CMRI	Median 2.2 years	In bivariate analyses, after adjustment for LVEF, presence of LGE, RV LGE, and RV ^{18}F-FDG uptake were predictive of composite of death, aborted SCD, sustained VA, complete AVB, and HF hospitalization.
Sperry et al. 2018[323]	203 patients with suspected CS. 46% had normal findings on ^{18}F-FDG PET	Mean 1.8 years	Heterogeneous ^{18}F-FDG uptake and the summed score of abnormal perfusion and ^{18}F-FDG uptake in different myocardial segments were predictive of death, transplantation, or VT requiring defibrillation

AVB indicates atrioventricular block; CS: cardiac sarcoidosis; CMRI: cardiac magnetic resonance imaging; HF: heart failure; HRS: Heart Rhythm Society; ICD: implantable cardioverter defibrillator; JCS: Japanese Circulation Society; JMHW: Japanese Ministry of Health and Welfare; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; NPV: negative predictive value; RV: right ventricular; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography

2.11.3 Advanced cardiac imaging

2.11.3.1 Cardiac magnetic resonance imaging

CMRI is the most accurate method for assessing ventricular function, the well-known but, as mentioned above, insensitive predictor of adverse events. Most studies have focused on other, potentially more accurate CMRI parameters (see Table 11). There are multiple studies reporting that the presence (vs. absence)[93,307,316] or quantity of LGE[28,30] is associated with adverse events in known or suspected CS, and that LGE clearly outweighs LVEF as an outcome predictor. For example, Murtagh et al.[28] studied 205 sarcoidosis patients and concluded that increased LGE burden combined with RV dysfunction identified patients with the highest risk of death and/or VT. It should be noted that only a fifth of these patients probably had true CS, as only 20% of cases exhibited LGE on CMRI.[28] Several other studies have likewise analyzed populations consisting of patients with extra-cardiac sarcoidosis having suspected CS or undergoing routine CMRI screening for cardiac involvement (Table 11). In these studies, the prognostic significance of LGE is most probably explained by the fact that pathological LGE identifies the true CS subpopulation.

2.11.3.2 ^{18}F-fluorodeoxyglucose positron emission tomography

In recent years, several studies, summarized in Table 12, have studied the prognostic role of ^{18}F-FDG PET in CS. In a study by Blankstein et al., the presence of focal perfusion defects with abnormal ^{18}F-FDG uptake was associated with a significantly higher risk of death or VT.[182] Another study of 203 patients with suspected CS showed that the heterogeneity of metabolism on ^{18}F-FDG PET (quantified using the coefficient of variation of ^{18}F-FDG uptake), and the summed score of abnormal perfusion and ^{18}F-FDG uptake in different myocardial segments were predictive of death, transplantation, or VT.[323] In contrast, in the study by Bravo et al., ^{18}F-FDG PET offered no additive prognostic information on top of LGE CMRI.[322]

2.11.4 Programmed ventricular stimulation

Aizer et al.[311] reported that in 32 patients with sarcoidosis and suspected cardiac involvement, inducible VAs were associated with future ICD therapies or SCD (HR 4.47, 95%CI 1.30 to 15.39). Inducible VAs were also predictive of future arrhythmic events in the 26 patients without previous spontaneous VTs (HR 6.97, 95%CI 1.27 to 38.27). The mean LVEF was < 35% in both PVS-positive and PVS-negative group. Also, two (10%) patients without previous spontaneous or inducible VAs still had sustained VAs or SCD during follow-up. In another study[101] with 19 CS patients undergoing PVS, six out of eight patients with positive PVS had a later VT

or VF. The median LVEF in this group was 38%. The median LVEF in the PVS-negative group was significantly higher, at 61%. One of the 11 (9%) PVS-negative patients had a sustained VT during follow-up, suggesting a negative predictive value of PVS for an arrhythmic event of 91%. Mehta et al.[306] studied the usefulness of PVS in risk stratification in 76 CS patients without a history of spontaneous VAs. During a median follow-up of five years, six out of eight (75%) patients in the PVS positive group had an arrhythmic event or died compared to one death from respiratory failure in the PVS negative group ($p < 0.0001$). It is noteworthy that the mean baseline LVEF was 36.4±4.2 in the PVS positive group and 55.8±1.5 in the PVS negative group. Thus, the additional benefit of PVS in risk stratification in this cohort, after estimation of LV function, remains unclear. Another study of 25 patients with probable or definite CS and abnormal myocardial LGE or ^{18}F-FDG uptake, reported a 100% positive predictive value for positive PVS.[324] One of 10 patients with LVEF > 35% and no prior VAs had a VA during follow-up.

In conclusion, inducible VAs by PVS during an invasive electrophysiological study are associated with the occurrence of future clinical VAs in CS. It is however somewhat unknown if PVS provides additive prognostic value over LVEF estimation. Even more importantly, it is unclear if a baseline negative PVS can be relied upon to omit ICD implantation.[101,306,311,324]

2.12 Prognostic factors in giant cell myocarditis

Aside from the works of the present thesis, no other studies specific to the predictors of outcome in GCM exist.

2.13 Implantable cardioverter defibrillator indications in cardiac sarcoidosis and giant cell myocarditis

An ICD can be considered to improve prognosis in selected patients with CS or GCM by preventing an arrhythmic SCD. Evidence from controlled studies is lacking, however, and the decisions to implant, for primary prevention in particular, are not straightforward. The benefits of ICD are mitigated by the risk of device complications,[325] including inappropriate shocks,[16,310,312] and by ICD's psychological effects.[326] Overall, roughly one fifth of CS patients receive inappropriate ICD shocks,[327] with the annual risk, attributable mainly to supraventricular arrhythmias, being 4.1–5.7%.[16,310,312] In GCM, there is little data specific to the therapeutic role of ICD implantations.[3,6,13] As fatal or aborted SCDs are not uncommon,[7] implantation appears worthy of consideration if the disease

course is not fulminant and prospects for survival without urgent transplantation are favorable. Table 13 summarizes the current ICD indications in CS by the HRS 2014 and the AHA/ACC/HRS 2017 recommendations. The main difference is the inclusion of the presence of myocardial scar on CMRI or PET as a Class IIa ICD indication in the 2017 consortium guidelines. Another significant difference is that the consortium guideline does not require a trial of immunosuppression prior to implantation in patients with an LVEF ≤ 35%, a view shared by other experts.[328] The JCS has published national recommendations for the use of ICD in Japan, which are clearly more restrictive and are not dealt with in detail here.[80] There is little experience of wearable cardioverter defibrillators in CS or GCM.[329] Such a device might, however, be useful as a bridge to transplantation,[330] in cases with a delay in obtaining definitive diagnosis,[331] and in patients with a temporary contraindication (e.g., infection) for an ICD implantation.[332]

Table 13. Summary of recommendations for ICD implantation in CS

	HRS 2014[83]	AHA/ACC/HRS 2017[260]
Class I†	1. Spontaneous sustained VAs, including prior aborted SCD 2. LVEF ≤ 35%, despite OMT and a period of immunosuppression (in patients with active inflammation).	CS patients with sustained VT or aborted SCD or LVEF ≤ 35%, if meaningful survival greater than one year is expected
Class IIa†	Independent of ventricular function and one or more of the following:	CS patients with expected meaningful survival > 1 year with LVEF > 35% and one or more of the following:
	1. An indication for PM	1. Syncope
	2. Unexplained syncope or near-syncope felt to be arrhythmic in etiology	2. Evidence of myocardial scar by CMRI or ^{18}F-FDG PET‡
	3. Inducible VAs in PVS	3. Inducible VAs in PVS
Class IIb†	LVEF 36%–49% and/or an RVEF < 40%, despite OMT for HF and a period of immunosuppression (in patients with active inflammation).	
Class III†	ICD is not recommended in patients with 1. No history of syncope, normal LVEF/RVEF, no LGE on CMRI, a negative PVS, and no indication for PM. 2. Incessant VAs or severe NYHA class IV HF	

†Class I indicates that the management "is recommended"; Class IIa, "is reasonable", Class IIb, "might be reasonable" and III "is potentially harmful".

‡Both "scar" and "extensive scar" are used interchangeably in the guideline without specific definition of the latter

CMRI indicates cardiac magnetic resonance imaging; CS: cardiac sarcoidosis; HF: heart failure; ICD: implantable cardioverter defibrillator; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; OMT: optimal medical therapy; PM: permanent pacemaker; PVS: programmed ventricular stimulation; RVEF: right ventricular ejection fraction; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia; ^{18}F-FDG PET: ^{18}F-fluorodeoxyglucose positron emission tomography

3 AIMS OF THE STUDY

The initial focus of this thesis was to study the incidence and risk factors of life-threatening VAs and the risk of SCD in CS and GCM. During the work, several cases of CS mistaken for GCM were detected and an additional aim was set to study the relationship and differential diagnostics of CS and GCM.

Specifically, the aims were:

- To study the occurrence of SCD both as the first presenting manifestation and as the mode of death in CS (IV) and GCM.
- To analyze the incidence of life-threatening VAs and their predictors in CS (I) and GCM (III).
- To evaluate survival in CS (IV) and GCM (II)
- To investigate the reasons for mistaking CS for GCM and to compare the characteristics, survival, and incidence of life-threatening VAs in "true" GCM vs CS initially mistaken for GCM (V, IIb, IIIb).

4 STUDY COHORTS, MATERIALS, AND METHODS

4.1 MIDFIN registry

The MIDFIN study group is a cardiology research network of Finland's five university hospitals focusing on CS and GCM. Since 2008, it has maintained a regularly updated nationwide registry of CS and GCM patients seen in the university hospitals and in provincial hospitals providing tertiary cardiac care. This web-based registry is accessible from the participating hospitals by a two-step authentication process. It includes patients diagnosed from the late 1980s onwards with data on their demographics, symptoms, clinical manifestations, results of diagnostic imaging and laboratory studies, invasive procedures, details of treatment, and adverse events including mortality and cause of death determined by hospital chart review. Specifically, the collected imaging data included echocardiographic LVEF as well as information on the presence of ^{18}F-FDG uptake on PET and LGE on CMRI. Laboratory studies collected included the results of cTnT/I and NT-proBNP measurements. The assigned cardiologists and/or research assistants from the participating hospitals regularly update the registry for incident cases and for data from the routine clinical follow-up visits of prevalent cases. The registry was founded in 2008 and collection of data from 1988 up to 2008 was therefore fully retrospective. All cases diagnosed as CS, presenting from 1998 through 2015, and cases initially diagnosed as GCM, presenting from 1991 through 2015, were included in this thesis. Five CS cases included in the MIDFIN registry prior to 1998 were omitted from the present work to ensure temporal parallelism with data from the cause-of-death registry (see section 4.2 below).

4.2 Cause-of-death registry

In Finland, a death certificate stating the main cause of death is issued for every deceased person. A medicolegal investigation into the cause of death is mandatory by law in all cases where the deceased has not been under the care of a physician during their last illness, death is not due to a known disease, or is otherwise unexpected or non-natural. Text bodies of the death certificates from the national cause-of-death registry are available in digital format from 1998 onwards. To detect cases of CS and GCM escaping a lifetime diagnosis, we searched the database for cases where the primary cause of death was documented with the ICD-10 code D86.8+I41.8 (CS) as well as for cases where the cause of death was coded as D86 (sarcoidosis), I51.4 (myocarditis, unspecified), or I40 (acute myocarditis)

and either the phrases “cardiac sarcoidosis” or “giant cell myocarditis” were present in the text body of the death certificate. The registry search covered the timespan from 1998 through 2015. We excluded cases that were already included in the MIDFIN registry at the time of the database search, as well as cases where histological material could not be acquired for re-examination. For the remaining cases, all histological material available from autopsies was re-examined. The written autopsy reports were scrutinized for observations of other cardiac diseases and extracardiac organ involvement of sarcoidosis.

4.3 Diagnostic criteria

4.3.1 Cardiac sarcoidosis

For CS, we adhered to the diagnostic criteria advocated in the HRS expert consensus statement[83] as well as in the WASOG diagnostic instrument for CS.[84] The diagnosis of CS required documentation of sarcoidosis histology in a sample of myocardium (the preference), or in extracardiac tissue, combined with clinical cardiac manifestations and abnormalities in cardiac imaging. Findings indicative of cardiac involvement on echocardiography included ventricular wall abnormalities and depressed LVEF. Typical CMRI findings included patchy LGE patterns not conforming with coronary artery distribution and local ventricular wall abnormalities. Typical ^{18}F-FDG PET findings included focal myocardial ^{18}F-FDG uptake with or without perfusion defects. The histological criteria for sarcoidosis were the presence of non-necrotizing epithelioid cell granulomas with giant cells and no more than solitary eosinophils without extensive myocardial necrosis.

4.3.2 Giant cell myocarditis

For studies II and III, the diagnosis of GCM required myocardial histology showing myocyte injury with or without necrosis associated with multinucleated giant cells and an inflammatory infiltrate variably composed of lymphocytes, histiocytes, and eosinophils. The presence of well-formed granulomas excluded the diagnosis of GCM. The available diagnostic myocardial samples for patients in studies II and III were verified by two cardiac pathologists applying the criteria above. In two cases, the original samples were unavailable for reanalysis. One of the two diagnoses was based on autopsy and the other on EMB. The available histology reports described findings typical for GCM by experienced pathologists and both cases were retained in studies II and III.

For the later re-evaluation of GCM diagnoses (see sections 4.4 and 5.1), the histological criteria for GCM were identical to the ones used previously for studies II and III with the exception that the presence of any myocardial granulomas recognizable with reasonable certainty, including the immature ones identified with the help of immunohistochemistry, were considered diagnostic of CS and exclusive of GCM. Furthermore, cases where extracardiac histology confirmed or ^{18}F-FDG PET strongly suggested the presence of systemic sarcoidosis were reclassified from GCM to CS, even in the absence of myocardial granulomas.

4.3.3 Grading of myocardial injury (studies II and III)

Two cardiac pathologists re-analyzed in retrospect all material available from the diagnostic myocardial biopsies of patients included in original studies II and III. The extent of cardiomyocyte necrosis and the number of eosinophils were graded visually on hematoxylin-eosin–stained samples using a semiquantitative four-point scale (0, 1, 2, and 3 for none, mild, moderate, and severe, respectively). The extent of myocardial fibrosis was scored in a similar manner on slices stained with Masson's trichrome. All scores were based on the pathologists' consensus. Figure 9 demonstrates the grading of myocardial necrosis and fibrosis.

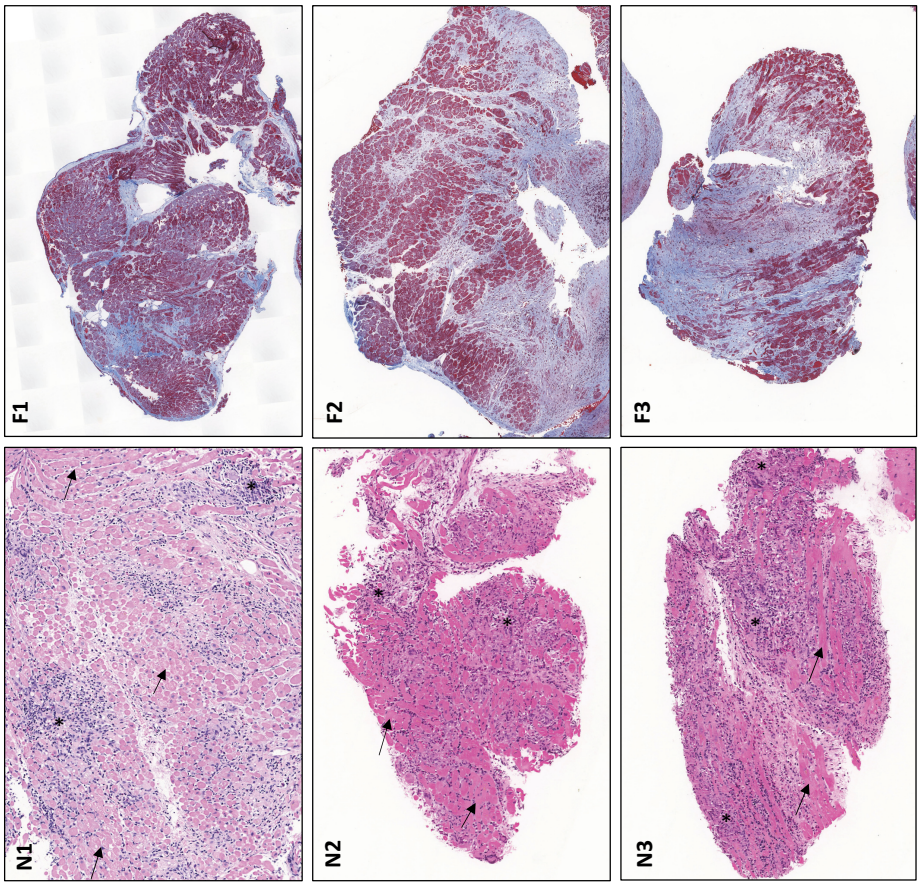

Figure 9. Grading of the extent of myocardial necrosis (left panels) and fibrosis (right panels). Myocardial necrosis was graded from hematoxylin- and eosin-stained slices. Panel N1 represents mild, N2 moderate, and N3 severe myocardial necrosis, respectively. Gradually less normal myocytes (black arrows) with an increasing amount of necrosis (asterisk) are seen from panel N1 through N3. The grading of fibrosis was based on Masson's trichrome-stained histological samples showing fibrosis in blue. Examples of mild (F1), moderate (F2), and severe (F3) myocardial fibrosis are shown. The scores given for necrosis and fibrosis were a result of the consensus of two cardiac pathologists, based on visual estimation. The original magnification coefficient is 100x (objective 10x, ocular tube 10x) in panels F1–F3 and 200x (objective 20x, ocular tube 10x) in panels N1–N3.

4.4 Re-evaluation of giant cell myocarditis diagnoses

In 2018, while working on Study IV, we came across several cases of CS that had initially been mistaken for GCM. As it was apparent that this problem could also involve the GCM populations of our earlier works (studies II and III), we decided to re-evaluate each GCM diagnosis made during the period covered by the present thesis. For the review of the GCM cases from the MIDFIN registry, we acquired all histologic material still available from the original diagnostic myocardial biopsies as well as any specimens available from follow-up myocardial biopsies, explanted or autopsied hearts, or extracardiac tissues. In addition to microscopy, we also used other information pertinent to the differentiation of CS from GCM, including imaging studies with either ^{18}F-FDG PET or plain chest CT. The acquisition of review material for cases from the cause-of-death registry is described above in section 4.2. The histopathological re-evaluation of all GCM cases was made by two examiners having > 10 years of experience in cardiovascular pathology. Their consensus was needed to convert the diagnosis of GCM to CS in clinicopathological meetings with the cardiologists involved in studies II and III.

4.5 Study population

This thesis included 351 cases of CS with disease presentation in Finland from 1998 through 2015 and 29 cases of GCM presenting from 1991 through 2015.

4.5.1 Cohorts in studies I–V

- Study I: all CS patients seen in Helsinki University Hospital from Feb 2004 through 2014 with sufficient quality CMRI studies and absence of CAD (n=59). These patients also constitute a subgroup of Study IV.
- Study II: all cases with an initial diagnosis of GCM seen in Helsinki University Hospital from 1991 through May 2015 (n=46).
- Study III: the 46 patients of Study II with five additional cases diagnosed until January 2016.
- Study IV: 351 adult (> 18 years) CS cases presenting from 1998 through the end of 2015. Of them, 263 cases were identified from the MIDFIN registry and 61 from the cause-of-death registry; the remaining 27 were initially misdiagnosed as GCM in the MIDFIN registry and later reclassified as CS (see sections 4.4 and 5.1).
- Study V: 73 adult (> 18 years) patients with a diagnosis of GCM at the start of our re-evaluation study in 2018. Of these, 49 came from the MIDFIN registry and 24 from the cause-of-death registry.

4.6 Data collection

For studies I–III and V, I reviewed the pertinent hospital charts for patients' symptoms, initial and later disease manifestations, diagnostic laboratory and imaging examinations, treatment and its complications, and occurrence of adverse events up to the end of 2015. For Study IV, I collected the above information from the database of the MIDFIN registry and from the autopsy reports and hospital charts of CS patients diagnosed only at autopsy.

The collected laboratory data included measurements of cTnT and NT-proBNP taken and analyzed as part of clinical routine. The collected imaging data included LVEF by echocardiography, presence of ^{18}F-FDG uptake on PET and of LGE on CMRI, as well as findings of coronary angiography. The CMRI studies of patients in Study I were re-analyzed in detail for the purposes of the present research (see section 4.7). For patients in studies II and III, I scrutinized the available ICD reports and collected the details of appropriate and inappropriate ICD therapies.

In study V, data from studies II and III were used with the addition of details collected from the autopsy reports and hospital charts pertinent to the GCM cases diagnosed postmortem. The histological material was reanalyzed as described above. I determined the causes of death from hospital charts and/or from autopsy reports. The data collection was mainly retrospective and took place between 2013 and 2018.

4.7 Analysis of cardiac magnetic resonance imaging studies

Analysis was performed using dedicated software (QMass MR 7.60.30.0; Medis). LV and RV volumes and LV mass were derived by manually drawing LV endo- and epicardial contours and RV endocardial contours on all short-axis slices from base to apex at end-diastole and end-systole. Papillary muscles and endocardial trabeculations were regarded as part of the ventricular cavity. LV wall thickness was calculated and the presence of marked basal septal thinning (< 4mm) was separately noted. Separate regions of interest representing healthy myocardium free of LGE and myocardium with intense LGE were drawn on a slice optimally distinguishing healthy from diseased heart muscle. The extent of LGE as a percentage of LV mass was then automatically calculated using the full width at half maximum method[333] for defining the threshold for LGE (Figure 10). The presence of edema was analyzed from T2-weighted images. Edema was defined as myocardial signal intensity > 1.9-fold the intensity in the skeletal muscle and classified as either present or absent. I personally analyzed all CMRI studies. To assess the repeatability of image analysis, an independent expert and I later blindly re-analyzed 10 randomly selected studies. The Bland-Altman method was used to calculate the repeatability coefficients for intra- and interobserver measurements.

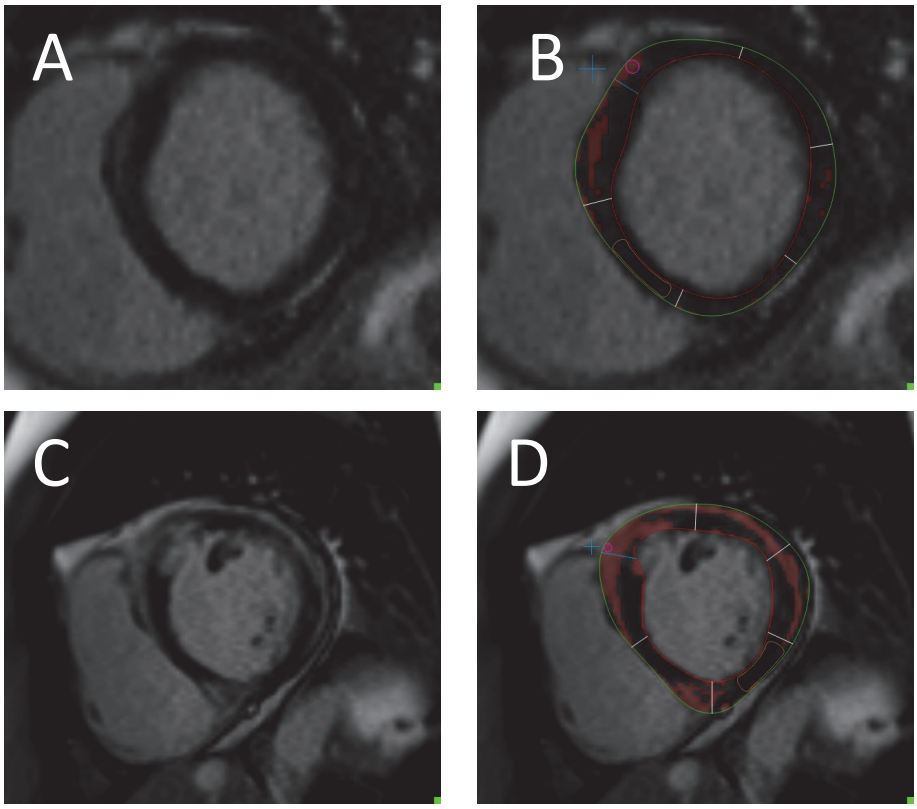

Figure 10. Examples of mild (panels A and B) and extensive (panels C and D) late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMRI).

Panels A and C show selected mid-ventricular LGE-CMRI short-axis slices with mid-myocardial LGE. Panels B and D are the same slices with LGE semi-automatically quantified and painted in red. The global LGE extent (percentage of LV volume) by the full-width half-maximum method (see methods section 4.7) was 8% and 27% in the patients with representative images shown in panels A/B and C/D, respectively.

4.8 Definitions of study endpoints

The outcome endpoint for Study I was a composite of death from cardiac cause, transplantation, or life-threatening VA, whichever came first. Life-threatening VA was defined as (1) SCD; (2) aborted SCD, that is, VF defibrillated successfully either by an ICD or externally during resuscitation; or (3) VT requiring ICD therapy or synchronized external cardioversion or defibrillation. The endpoint for studies II and V was a composite of death or cardiac transplantation. For Study III, the primary endpoint event was SCD (fatal or aborted), and the secondary endpoint event was a composite of SCD or any life-threatening VA. In Study IV, the endpoint event was death from any cause. Considering the information available to us of

the circumstances of death, the fatal event was classified as SCD if the witnessed prodromal symptoms had lasted < 24 hours (instead of the < 1 hour definition) and the victim arrested and died immediately at the scene or was primarily successfully resuscitated from cardiac arrest but died later without neurological recovery. An unwitnessed death was considered SCD if CS or GCM was the only cardiac pathology at autopsy and the available medical history together with autopsy findings and other medicolegal studies (including toxicology) excluded other causes of death.

4.9 Ethical aspects

The MIDFIN registry study gained the approval of the national ethical review board from 2009 (STM/1219/2009). The study of fatalities in CS and GCM was approved by the ethical review board in 2015 (317/13/03/01/2015). Two Finnish governmental authorities, the National Authority for Medicolegal Affairs (4615/06.01.03.01/2016) and the National Institute for Health and Welfare (THL/691/5.05.00/2016) approved the study of cases from the cause-of-death registry and the review of postmortem autopsy material. The studies were conducted according to the Declaration of Helsinki. The patients gave their informed, written consent to data collection for the national MIDFIN registry.

4.10 Statistical analyses

Continuous variables are presented as mean value ± standard deviation when sample distribution was symmetric, and median (minimum – maximum or interquartile range) when sample distribution was skewed. Categorical variables are presented as absolute numbers and percentages. The Pearson r was calculated when testing for linear correlation between two continuous variables. Comparisons between groups were performed using x^2 statistics for categorial variables and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. In all tests, a two-tailed $p < 0.05$ was considered statistically significant.

The time point of GCM diagnosis was defined as the date of myocardial biopsy confirming the diagnosis of GCM. Survival time was calculated from the date of onset of symptoms compatible with CS or GCM (studies II–V) or from the date of CMRI study (Study I). Survival curves were plotted and survival estimates were calculated by the Kaplan-Meier method. Cause-specific cumulative incidence analysis was used to plot the incidence–time curves. Between-group comparisons were made by the log rank test for the Kaplan-Meier method and by the Gray test for the cumulative incidence analysis. HRs and subdistribution

HRs were calculated by Cox regression analysis and by the Fine and Gray model, respectively. In cumulative incidence analysis and the Fine and Gray model, cardiac transplantations and deaths caused by terminal HF were considered competing events. The validity of proportional hazards assumption was tested by calculating Schoenfeld (partial) residuals and plotting them against follow-up time. The assumption was considered valid if no statistically significant time-dependent correlation was observed. The analyses were performed using SPSS versions 22.0–24.00 for Macintosh (SPSS Inc.; Chicago, IL, USA), Xlstat Biomed (Addinsoft, Paris, France) and R software (R Development Core Team).

5 RESULTS

5.1 Re-evaluation of giant cell myocarditis diagnoses

At the end of 2015, the MIDFIN registry included 51 cases of GCM collected from 1991 onwards. These patients constituted the population of Study III, and 46 of them (until May 2015) constituted the population of Study II. After the full re-evaluation work, the diagnosis was converted to CS in as many as 27/51 (53%) instances, the reasons being as follows. In 20 cases originally missed myocardial granulomas were found, varying from occasional well-formed follicular structures to granulomas in different earlier stages of development (Figure 11). In one case transplanted in 2018, abundant granulomas had been noted in the routine clinical explant study and the diagnosis was converted to CS. In two more cases transplanted for GCM, re-evaluation of specimens available from the native hearts revealed granulomas that had been missed in the original explant study. In one further post-transplant case, follow-up allograft biopsies showed a recurrence of disease with granulomas diagnostic of CS escaping recognition in routine clinical practice. Immature myocardial granulomas had been detected during original diagnostic work-up in one case but the initially assigned diagnosis was still GCM. In one case, sarcoid granulomas were found on the microscopy of renal tissue and finally, in one case with poor-quality original myocardial specimens, ^{18}F-FDG PET-CT taken at presentation showed extracardiac inflammatory activity (mediastinal lymph nodes and lungs) favoring the diagnosis of CS.

Screening of the cause-of-death registry exposed 24 cases of GCM diagnosed at autopsy by forensic (n=21) or general (n=3) pathologists until the end of 2015. After the re-evaluation, a total of 19 of these cases (79%) were reclassified as CS. In nine of them, myocardial granulomas had been missed in the initial autopsy study (Figure 12), while in 10 cases, either extra-cardiac or cardiac granulomas had been detected but the assigned diagnosis was still GCM. The most common sites for the extracardiac granulomas were mediastinal lymph nodes, lungs, kidneys, and liver (Figure 13).

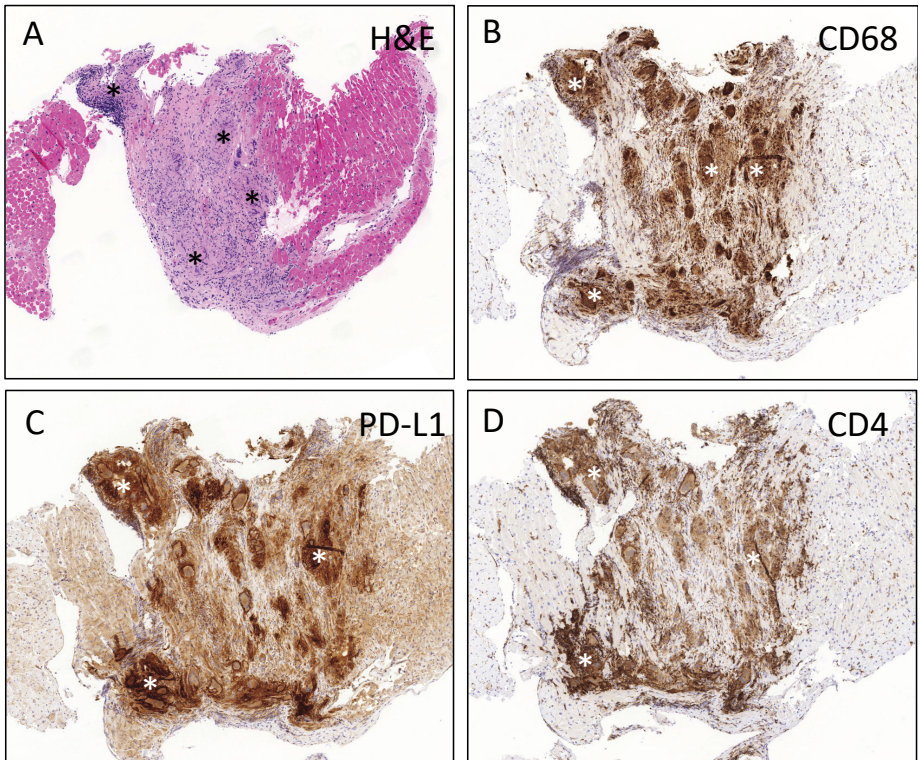

Figure 11. Detection of immature granulomas.

Hematoxylin eosin-stained myocardial tissue shows dense lymphocytic infiltrate with paler areas (black asterisk) representing immature granulomas (A). Immunohistochemical staining for markers of CD68 (B), PD-L1 (C), and CD4 (D) highlight the granulomas (white asterisk). The magnification coefficient is 100x (objective 10x, ocular tube 10x) in all microphotographs.

Taken together, more than half (46/75, 61%) of all cases diagnosed initially as GCM during the study period were reclassified as CS. The results of the original analyses, done before the re-evaluation and reclassification of cases, are reported in the original articles (studies II and III) but all results reported in this thesis from here on are based on final (i.e., corrected) diagnoses.

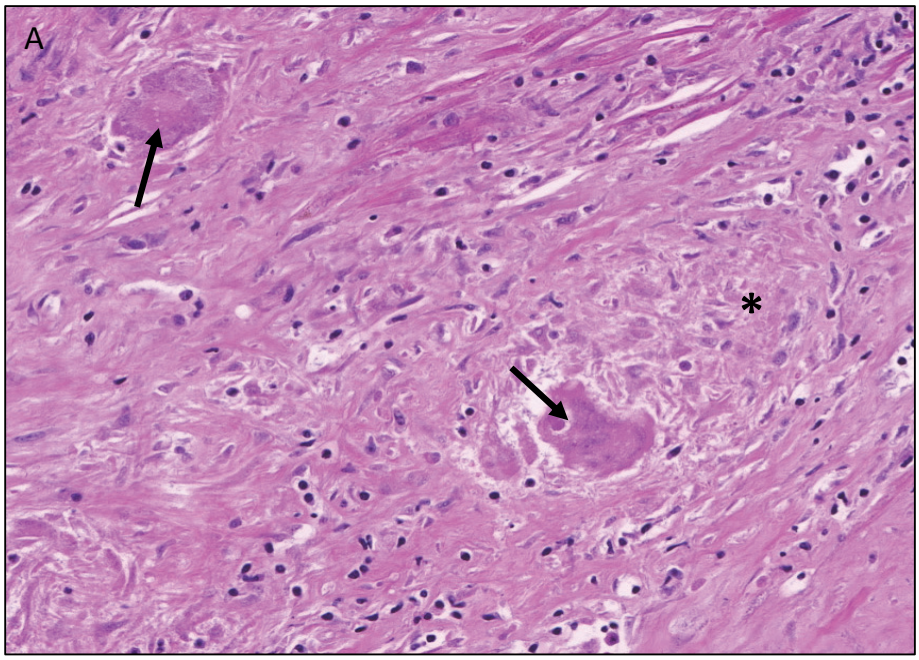

Figure 12. Autolysis complicating the recognition of myocardial granulomas.

In a post-mortem myocardial sample, tissue autolysis causes giant cells to lose nuclei (black arrows) and granulomas (asterisk) become less evident. The original magnification coefficient is 400x (objective 40x, ocular tube 10x).

5.2 Characteristics of the study population

5.2.1 Cardiac sarcoidosis

A total of 351 incident cases of CS, 253 females and 98 males, with a mean age of 52±12 years, were included in the study. Figure 14 shows their temporal distribution over the study period and Table 14 summarizes their key characteristics at the time of disease presentation. The diagnosis was absolute (i.e., based on myocardial histology) in 221 cases (63%), being made from lifetime diagnostic biopsies in 149 cases, at autopsy in 62 cases, and at the post-transplant study of the native heart in 10 cases. In the remaining 130 cases, sarcoid histology was confirmed from biopsies of lymph nodes or solid organs in 104 and 26 cases, respectively. At presentation, extra-cardiac sarcoidosis was detected in 98 patients. Subsequent investigations during follow-up revealed extra-cardiac involvement in 127 additional patients. Patients with a lifetime diagnosis of CS (n=289) were younger at the time of presentation compared to patients diagnosed only at autopsy (50±10 vs. 57±16; p=0.004). A trend toward more females in the lifetime-diagnosis group was observed (74% vs 65%; p=0.059). Of all 351 CS patients, 237 were screened

for CAD either by invasive or CT coronary angiography, or at autopsy. Significant CAD, defined as more than 50% stenosis in the left main stem, proximal left anterior descending branch or in at least 2 main epicardial arteries, was present in eight cases, five of which were detected at autopsy.

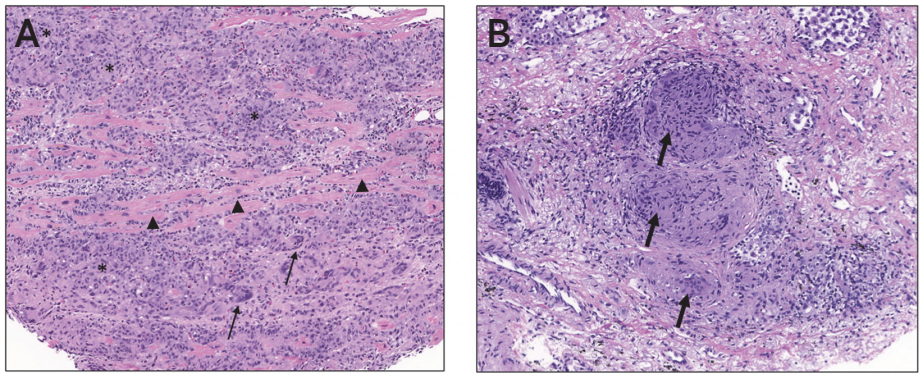

Figure 13. Conversion of the diagnosis from GCM to CS based on study of extracardiac tissue. Endomyocardial biopsy (A), demonstrated wide myonecrosis (asterisk), with few preserved myocytes (arrowhead), giant cells (thin arrow) and eosinophilia, suggesting a diagnosis of GCM. However, microscopy of lung biopsy showed distinct non-caseating, well-formed epithelioid granulomas (thick arrow) diagnostic of sarcoidosis (panel B). The original magnification coefficient is 200x (objective 20x, ocular tube 10x) in both panels.

As Table 14 shows, high-degree AVB was the most common presenting manifestation (42%) followed by HF (17%). SCD without preceding symptoms, fatal or aborted, was the first and only manifestation in 14% of all CS cases. Of the 38 patients presenting with fatal SCD, 29 died at home. Sixteen of these SCDs were witnessed, seven were associated with physical exertion, and autopsy revealed concomitant severe CAD in four cases.

A total of 24 patients with a post-mortem diagnosis of CS had presented with lifetime symptoms attributable to CS in retrospect. Each of them had undergone diagnostic studies, outlined in Table 15, but escaped lifetime diagnosis. Their median survival from onset of symptoms was 1.2 years (range 0.1–11.7).

Table 14. Characteristics of the CS Population at Presentation

	All cases N=351
Age (at presentation)	52±12
Female	253 (72)
Presenting manifestation	
AVB (third degree or Mobitz II second degree)	147 (42)
LV dysfunction with heart failure	58 (17)
Sudden cardiac death	50 (14)
Fatal	38 (11)
Aborted	12 (3)
Sustained VT	48 (14)
Frequent ventricular extrasystoles	20 (6)
Syndrome mimicking myocardial infarction*	11 (3)
Exertional chest pain	3 (1)
Atrial tachyarrhythmia	4 (1)
Non-specific symptoms†	10 (3)
Imaging studies	
LV ejection fraction ≤ 50%	174/305 (57)
LV ejection fraction < 35%	51/305 (17)
LGE-CMRI	181 (52)
Abnormal myocardial LGE	171 (94)
^{18}F-FDG PET-CT	191
Abnormal cardiac ^{18}F-FDG uptake	165 (86)
Cardiac troponin T > 50 ng/L	51/244 (21)
Cardiac troponin T > 500 ng/L	12/244 (5)
NT-proBNP (ng/L)	866 (310–1900)
Associated diseases	
Diabetes	33 (10)
Hypertension	76 (24)
Severe CAD at angiography or autopsy‡	8 (2)
Severe renal failure (GFR < 30 mL/min/1.73^2)	4 (1)
Cancer	31 (10)

Data relates to number (%) of cases, medians (interquartile range), or mean ± standard deviation

*chest pain, ischemic ECG and normal coronary angiogram

†one or more of the following: unexplained syncope, elevated cardiac troponin, fatigue, dyspnea, or bundle-branch block on the electrocardiogram.

‡, defined as more than 50% stenosis in at least two main epicardial arteries, in the proximal left anterior descending branch, or in the left main stem

AVB indicates atrioventricular block; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CS: cardiac sarcoidosis; GFR: glomerular filtration rate; LGE-CMRI: late gadolinium enhancement cardiac magnetic resonance imaging; LV: left ventricular; NT-proBNP: N-terminal pro b-type natriuretic peptide; VT: ventricular tachycardia; ^{18}F-FDG PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography

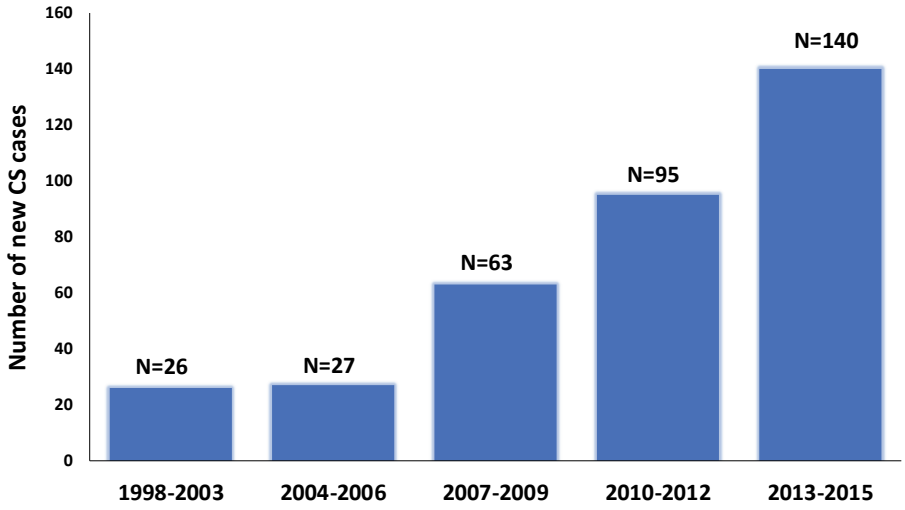

Figure 14. Temporal distribution of new cases of cardiac sarcoidosis (CS) from 1998 to the end of 2015

Table 15. Characteristics and diagnostic examinations of the 24 symptomatic CS patients escaping a lifetime diagnosis

	N=24
Age (at presentation)	57±13
Female	16(67)
Presenting manifestation	
AVB third degree or Mobitz II second degree	13(54)
Left ventricular dysfunction with heart failure	7(29)
Exertional chest pain	3(13)
Unexplained syncope	1(4)
Diagnostic studies	
Echocardiography	17 (LVEF < 50% in 11)
Coronary angiography	10 (all with normal findings)
LGE-CMRI	1 (widespread myocardial LGE)
^{18}F-FDG PET-CT	1 (myocardial perfusion defect without ^{18}F-FDG uptake)
Endomyocardial biopsy	2 (both non-diagnostic)

Data relates to number (%) of cases or mean±SD

AVB indicates atrioventricular block; CS: cardiac sarcoidosis; LGE-CMRI: late gadolinium enhancement cardiac magnetic resonance imaging; LVEF: left ventricular ejection fraction; ^{18}F-FDG PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography

5.2.2 Giant cell myocarditis

Altogether, 29 cases of GCM were included in the study, 20 females and nine males, with a mean age at presentation of 57±13 years. Figure 15 shows their temporal distribution over the study period and Table 16 presents their key characteristics at the time of presentation. The samples of myocardium for the study of histology had been obtained by EMB in 20 cases, at cardiac surgery in two cases, at the post-transplant study of the native heart in one case, and at autopsy in six cases. On reanalysis of the myocardial histology in the 21 GCM patients with material available from diagnostic lifetime biopsies, 10 patients (48%) had grade 2–3 (moderate to severe) myocyte necrosis and two patients (10%) had grade 2–3 myocardial fibrosis. Grade 2–3 myocardial necrosis and fibrosis did not overlap, and thus either of these findings was present in 12 (57%) patients. The number of eosinophils on biopsy material was graded 2–3 in 12 (57%) patients. None of the 29 patients had significant CAD.

A lifetime diagnosis was made in 22 (76%) patients with a median time from symptom onset to diagnosis of 0.3 months (range 0–4.6 months). HF was the most common presenting manifestation (45%) followed by AVB (21%) and SCD (14%). Three (50%) of the six patients with an autopsy diagnosis of GCM had presented with lifetime symptoms attributable to GCM in retrospect. Each of them had undergone diagnostic studies but escaped a lifetime diagnosis.

5.3 Treatment in brief

5.3.1 Cardiac sarcoidosis

Altogether, 276 of 313 CS patients presenting with lifetime symptoms received immunosuppressive therapy consisting of various combinations of corticosteroids (n=274), azathioprine (n=114), mycophenolate mofetil (n=20), cyclosporine (n=22), methotrexate (n=18), and infliximab (n=7). An ICD was implanted in 189 patients, and 77 patients received a permanent pacemaker. A total of 27 patients underwent cardiac transplantation, and RFCA of VT was done in 15 patients.

5.3.2 Giant cell myocarditis

Of 26 patients presenting with lifetime symptoms, 21 (81%) received immunosuppressive therapy. This consisted of corticosteroid monotherapy in seven patients and a combination of prednisolone, azathioprine, and cyclosporin in 14 patients. An ICD was implanted in 13 patients and a permanent pacemaker in six patients. Of the 13 patients with an ICD, 10 (77%) and three (23%) individuals received the device for primary and secondary prevention, respectively. Beta-blockers were used in 22 patients (85%), amiodarone in 14 patients (54%), and mexiletine in two (8%). RFCA of VT was done in three patients. An LV assist device was implanted in two patients and extracorporeal membrane oxygenator was used in three cases. Twelve patients underwent cardiac transplantation.

Table 16. Characteristics of the GCM population at presentation

	All cases
	N=29
Age	57±13
Female	20(69)
Presenting manifestation	
AVB third degree or Mobitz II second degree	6 (21)
LV dysfunction with heart failure	13 (45)
Sudden cardiac death	4 (14)
Fatal	3 (10)
Aborted	1 (3)
Sustained VT	3 (10)
Other*	3 (10)
Imaging studies	
LV ejection fraction < 35%	8/25 (32)
LV ejection fraction ≤ 50%	19/25 (76)
LGE-CMRI	12 (41)
Abnormal LGE	12 (100)
^{18}F-FDG PET-CT	2(7)
Abnormal ^{18}F-FDG uptake	2 (100)
Cardiac troponin T > 50 ng/l	18/20 (90)
Cardiac troponin T > 500 ng/l	16/20 (80)
NT-proBNP (ng/L)	5495 (2835–12309)
Associated diseases	
Other autoimmune disorders†	4(14)
Diabetes	2(7)
Severe CAD at angiography or autopsy‡	0
Severe renal failure (GFR < 30)	0
Cancer	1(3)

Data relates to number (%) of cases, medians (interquartile range), or means ± standard deviation

*syndrome mimicking myocardial infarction (n=1), elevated cardiac troponin, fatigue (n=1), and frequent ventricular premature beats (n=1).

†rheumatoid arthritis, hypo- or hyperthyroidism, celiac disease, Sjogren's syndrome, iritis, or ulcerative colitis

‡ defined as more than 50% stenosis in at least two main epicardial arteries, in the proximal left anterior descending branch, or in the left main stem

AVB indicates atrioventricular block; CAD: coronary artery disease; CMRI: cardiac magnetic resonance imaging; GCM: giant cell myocarditis; GFR: glomerular filtration rate; LGE: late gadolinium enhancement; LV: left ventricular; NT-proBNP: N-terminal pro b-type natriuretic peptide; VT: ventricular tachycardia; ^{18}F -FDG PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography

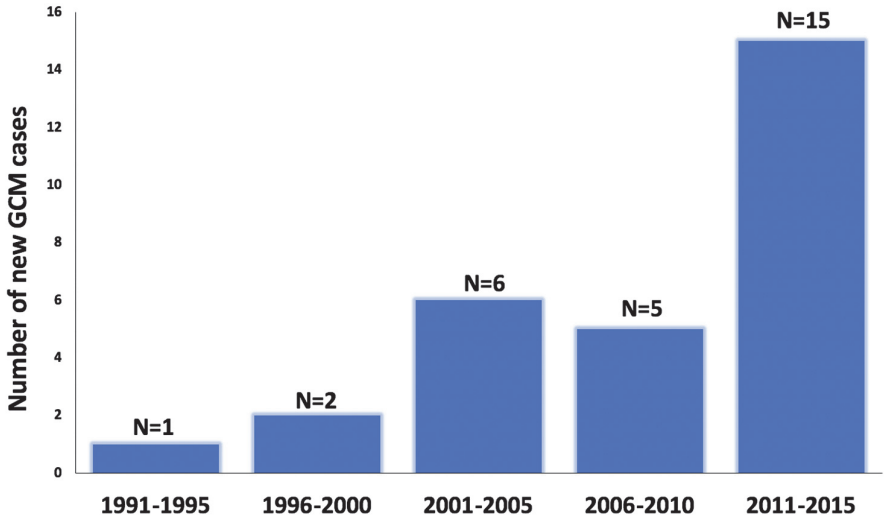

Figure 15. Temporal distribution of new cases of giant cell myocarditis (CGM) from 1991 to the end of 2015

5.4 Aspects of outcome in cardiac sarcoidosis and giant cell myocarditis

5.4.1 Modes of death and survival in cardiac sarcoidosis

Table 17. Modes of death in all 84 cases of fatal CS

Mode of death	All cases (N=84)
Sudden cardiac death	67(80)
Autopsy diagnosis, CS only	54(64)
Autopsy diagnosis, CS and CAD	5(6)
Lifetime diagnosis, CS only	7(8)
Lifetime diagnosis, CS and CAD	1(1)
Death due to heart failure	6(7)
Non-cardiac death	6(7)
Cancer	5(6)
Miliary tuberculosis	1(1)
Death post cardiac transplantation	5(6)
Acute rejection	1(1)
Chronic rejection	1(1)
Intracerebral bleeding	1(1)
Cancer	1(1)
Sepsis	1(1)

Data are number (%) of cases

CAD indicates coronary artery disease; CS, cardiac sarcoidosis

Of all 351 CS patients, 84 died during the study period. Table 17 details the different modes of death in these patients. Of note, 67 of all 84 fatalities (80%) were SCDs. Of the 313 patients presenting with cardiac symptoms during life, 46 (15%) died. Their follow-up time from symptom onset to death or end of study was 42 months (interquartile range 16–76 months). Only 22 deaths (26% of all) involved patients with a lifetime diagnosis of CS. Concomitant severe CAD was present at autopsy in six out of the 67 fatalities due to SCD. Table 18 shows the one-, five-, and 10-year Kaplan-Meier survival estimates for all CS patients presenting with lifetime symptoms (n=313) and separately for patients who were diagnosed with CS during life and received CS-targeted treatment (n=289). In the latter group, 98% of patients were estimated to survive beyond one year, and 93% beyond five years, from symptom onset.

Table 18. Kaplan-Meier survival estimates (95% confidence intervals) for the CS population

Estimate	All CS patients	Patients with lifetime CS diagnosis
	N=313	N=289
One year	95% (93–98)	98% (97–100)
Five years	85% (80–90)	93% (89–96)
10 years	76% (68–84)	87% (81–94)

CS indicates cardiac sarcoidosis

5.4.2 Cardiac magnetic resonance imaging as a predictor of outcome in cardiac sarcoidosis

Up until July 2014, a diagnostic CMRI study had been done in 59 CS patients treated at Helsinki University Hospital. For volumetric data analysis (ventricular volumes, wall thickness measurements, LVEF, and RVEF) we had to reject four cases due to insufficient image quality. For LGE analysis, nine cases had to be rejected, also due to insufficient quality of images. Until the end of April 2015 a total of 23 patients had reached the study's outcome endpoint, consisting of a composite of SCD (n=3), cardiac transplantation (n=1), and occurrence of life-threatening VA (n=19; VF in 5 patients and sustained VT in 14 patients).

CMRI variables associated with the study endpoint were RVEF (per 5% increment; HR 0.81, 95%CI 0.69–0.93; p=0.004), fraction of LGE from total LV mass (per tertiles; HR 3.06, 95%CI 1.56–6.04; p=0.001) and the presence of marked (< 4mm) thinning of basal interventricular septum (HR 3.64, 95%CI 1.31–10.12; p=0.013). Contrary to RVEF, LVEF was not predictive of the endpoint (HR 0.90, 95%CI 0.77–1.06; p=0.202). In a multivariate Cox regression model including RVEF, LGE extent and presence of marked septal thinning, LGE extent (per tertile) was the only independent predictor of the endpoint events (HR 2.22, 95%CI 1.07–4.59; p=0.032). The one-year estimate (95% CI) of event-free survival was 36% (12–60%) for patients in the highest LGE tertile (> 22% of LV mass) vs. 80% (66–95%) in patients with less LGE (log rank p < 0.001, Figure 16). The positive and negative endpoint predictive values of LGE > 22% were 75% and 76%, respectively.

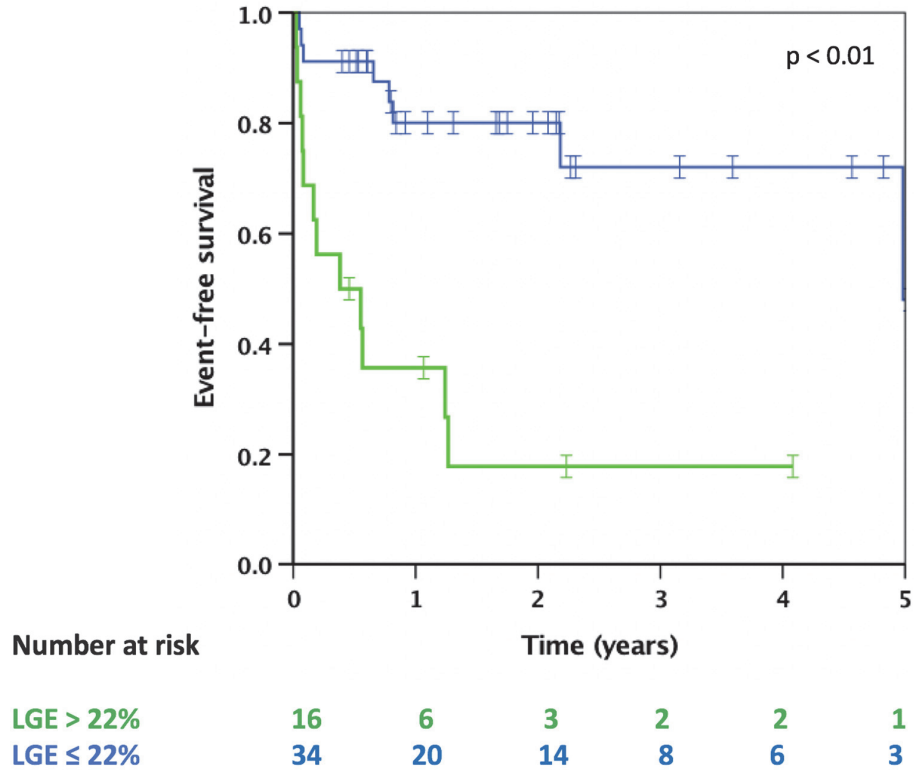

Figure 16. Kaplan-Meier curves for survival free of transplantation and life-threatening ventricular arrhythmias for patients with the extent of myocardial late gadolinium enhancement (LGE) in the highest tertile (green line) vs. in the rest (blue line).

5.4.3 Modes of death and survival in giant cell myocarditis

By the end of 2015, 11 GCM patients had died (all of cardiac causes) and 12 had undergone cardiac transplantation. Eight out of the 11 deaths involved patients diagnosed with GCM during life. SCD accounted for five (45%) fatalities, the other modes of death being HF in three (27%) and death postcardiac transplantation in three (27%) cases. The follow-up time from symptom onset to death, transplantation, or end of study ranged from 0.1 to 133 months (median, 6 months). Of the 12 transplantations, 10 were made because of intractable HF and two mainly because of VAs defying all therapies. Figure 17A shows the Kaplan-Meier graphs for both transplant-free and overall survival in the 26 patients presenting with lifetime symptoms. In these patients the one-, two- and five-year transplant-free survival estimates (95% CI) were 46% (26–65%), 37% (18–56%) and 26% (6–45%), respectively. The corresponding estimate of overall survival was 72% (54–90%), 67% (47–86%), and 67% (47–86%).

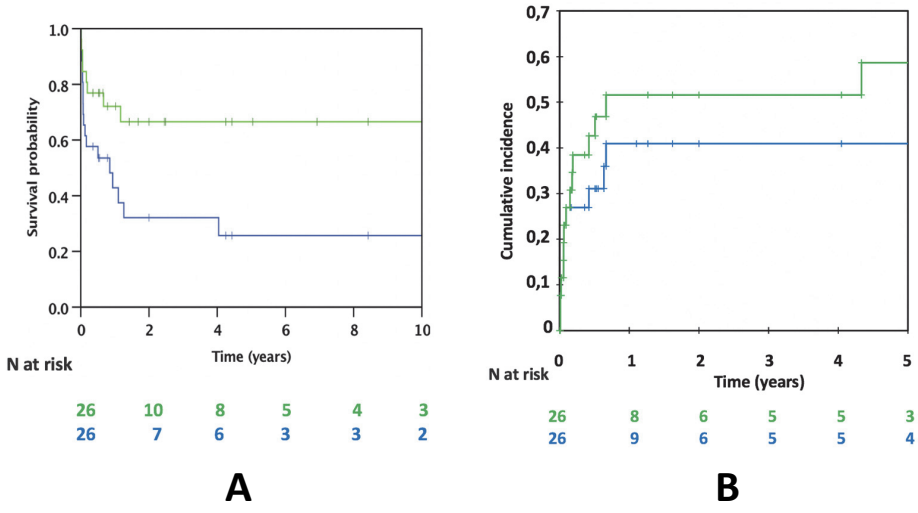

Figure 17. Panel A shows the transplantation-free (blue line) and overall (green line) survival in patients with giant cell myocarditis and lifetime presentation. Panel B shows the cumulative incidence of sudden cardiac death (SCD, blue line) and SCD or any life-threatening ventricular tachycardia (VT, green line) in these patients.

5.4.4 Incidence and characteristics of life-threatening ventricular arrhythmias in giant cell myocarditis

Figure 17B represents the cumulative incidences for both SCD (fatal or aborted) and SCD or any life-threatening VA in the 26 GCM patients presenting with lifetime symptoms. Apart from one late VT episode, all arrhythmic events occurred during the first year of follow-up. The cumulative incidence (95% CI) of either fatal or aborted SCD at one, six, and 12 months was 23% (11–47%), 31% (17–55%) and 41% (25–67%), respectively. The corresponding figures for SCD or any life-threatening VA were 23% (11–47%), 43% (27–67%) and 52% (35–76%).

From among the 13 patients with an ICD, 5 (38%) had one or several appropriate ICD therapies during follow-up. Detailed data from 19 episodes was available for review. The arrhythmia was classified by the ICD as monomorphic VT on all occasions. The ventricular rate ranged from 140 to 201 beats per minute (median, 180/min). When attempted by the ICD, antitachycardia pacing failed to convert VT in 6/16 (38%) episodes, of which one VT required two shocks and another episode required four consecutive shocks. No inappropriate shocks were observed.

Amiodarone was used to prevent recurrent symptomatic episodes of VAs in 14 (54%) cases. It produced a complete symptomatic remission in three patients, reduced the frequency of VT episodes in seven patients, and had no obvious effect in four patients. RFCA or surgical ablation of medically uncontrollable VT was

attempted in three patients. The procedures resulted in partial success as VT recurrences were abated in all patients though not abolished in any of them.

5.4.5 Factors predictive of outcome in giant cell myocarditis

Table 20 shows the results from univariate Cox regression analyses and Fine and Gray models of factors considered potential predictors of serious events in GCM. A worse transplant-free-survival was associated with the presence of biopsy evidence of either myocardial necrosis or fibrosis of a moderate-to-severe extent (p=0.013) and with elevated NT-proBNP (p=0.016). Moderate-to-severe myocardial fibrosis was also predictive of both fatal or aborted SCD (p=0.003) and any life-threatening VA (p=0.003) during follow-up. High cTnT (by tertiles) at presentation predicted the occurrence of SCD (p=0.014).

Table 19. Predictors of outcome in GCM

		HTx-free survival		SCD		SCD or VT
	e/n	HR (95%CI)	e/n	SHR (95%CI)	e/n	SHR (95%CI)
Age at presentation, per 1 year	17/26	0.99 (0.94–1.04)	10/26	1.05 (0.95–1.16)	14/26	1.05 (0.97–1.14)
Sex, male vs. female	17/26	1.00 (0.37–2.71)	10/26	0.44 (0.11–1.82)	14/26	1.12 (0.41–3.12)
LVEF per +5%	16/25	0.95 (0.77–1.18)	9/25	0.82 (0.67–1.00)	13/25	0.90 (0.76–1.08)
VT as presenting manifestation	10/26	1.15 (0.33–4.06)	10/26	0.51 (0.08–3.15)	14/26	1.52 (0.54–4.28)
NT-proBNP, per 1000 ng/L	10/19	1.08 (1.02–1.15)§	5/19	1.05 (0.99–1.11)	8/19	1.03 (0.94–1.11)
Cardiac Troponin T (per tertile)*	11/20	1.52 (0.68–3.40)	5/20	3.92 (1.32–11.63)§	9/20	1.51 (0.67–3.40)
Grade 2–3 myocyte necrosis or fibrosis†	12/21	7.14 (1.52–33.54)§	5/21	1.95 (0.39–9.67)	9/21	2.29 (0.63–8.32)
Grade 2–3 myocyte necrosis†	12/21	3.22 (0.95–10.86)	7/21	0.76 (0.18–3.20)	10/21	1.17 (0.36–3.84)
Grade 2–3 myocyte fibrosis†	12/21	5.32 (0.96–29.42)	7/21	6.52 (1.92–22.16)**	10/21	6.52 (1.92–22.16)**
Grade 2–3 eosinophils†	12/21	0.84 (0.26–2.72)	7/21	0.98 (0.23–4.25)	10/21	1.17 (0.34–3.98)
Use of triple drug immunosuppression‡	12/21	0.37 (0.12–1.15)	7/21	0.31 (0.07–1.30)	11/21	0.48 (0.16–1.47)

*First (0–1027 ng/L), 2nd (1028–2000 ng/L) and third (> 2000 ng/L) tertile

†The extents of necrosis and fibrosis on myocardial histology were graded using a four-point scale where 0, 1, 2, and 3 stand for none, mild, moderate, and severe, respectively

‡Combined use of prednisone, cyclosporine, and azathioprine from the onset of treatment (n=14) vs any other use of immunosuppressive drugs (n=7)

§$p < 0.05$

**$p < 0.01$

CI indicates confidence interval; e/n: the number of end point events per number of patients in the analysis; GCM: giant cell myocarditis; HR: hazard ratio from Cox regression analysis; HTx: cardiac transplantation; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro b-type natriuretic peptide; SCD: sudden cardiac death (including both aborted and fatal); SHR: subdistribution hazard ratio from Fine & Gray model; VT: ventricular tachycardia.

5.5 Comparison of cardiac sarcoidosis mistaken for giant cell myocarditis with the ultimate giant cell myocarditis cohort

5.5.1 Cases from the MIDFIN registry

The incidence of life-threatening VAs did not differ between the patients keeping the GCM diagnosis compared to patients reclassified as CS (Study IIIb). The cumulative incidence (95%CI) of life-threatening VAs at five years was 55% (28–75) in the 24 patients keeping the GCM diagnosis and 54% (30–73) in the 27 patients reclassified as CS, respectively (p=0.786). In bivariate Fine and Gray models with final diagnosis as the other variable, VT at presentation and moderate-to-severe myocardial fibrosis on microscopy were both independent predictors of life-threatening VAs; the SHR (95% CI) was 2.87 (1.37–6.03) for the former and 6.41 (3.17–12.94) for the latter.

5.5.2 All cases initially diagnosed as giant cell myocarditis in Finland

I compared the characteristics and survival of all 45 patients with CS initially diagnosed and treated as GCM with the 28 patients keeping the diagnosis of GCM after re-evaluation (status in 2018, study V). The GCM patients were older (58±10 years vs. 49±13 years, p=0.003), presented more often with HF (13/28 vs 9/45, p=0.017) and had higher circulating levels of cTnT (median 1239 ng/L vs. 50 ng/L, p < 0.001) and NT-proBNP (median 5273 ng/L vs. 1710 ng/L, p=0.007) at presentation.

Figure 18 depicts the Kaplan-Meier transplant-free survival curves and the cumulative incidence curves of SCD in the 34 GCM patients reclassified as CS and the 25 true GCM patients, all presenting with lifetime symptoms. In the former group, the one- and five-year transplant-free survival estimate (95%CI) was 82% (70–95%) and 46% (28–64%), respectively, while the corresponding figures for true GCM were 45% (24–66%) and 27% (7–47%). The difference was statistically significant (p=0.011). In a multivariate Cox regression analysis including diagnosis, age, and presentation with HF as explanatory factors, final CS diagnosis was an independent predictor of better transplant-free survival with a HR of 0.37 (95% CI, 0.17–0.81; p=0.013).

Instead, there was no statistically significant difference in the cumulative incidence of SCD between reclassified and true GCM (Figure 18B).

Of the 16 CS patients initially diagnosed with and treated for GCM with drugs including cyclosporine, six individuals (38%) developed impaired renal function (glomerular filtration rate < 60 mL/min/m2) and one (6%) developed severe renal failure (glomerular filtration rate < 30 mL/m2/min). One (6%) patient

suffered from recurrent diverticulitis which was considered a complication of immunosuppressive therapy. No malignancies were seen in these 16 patients during follow up.

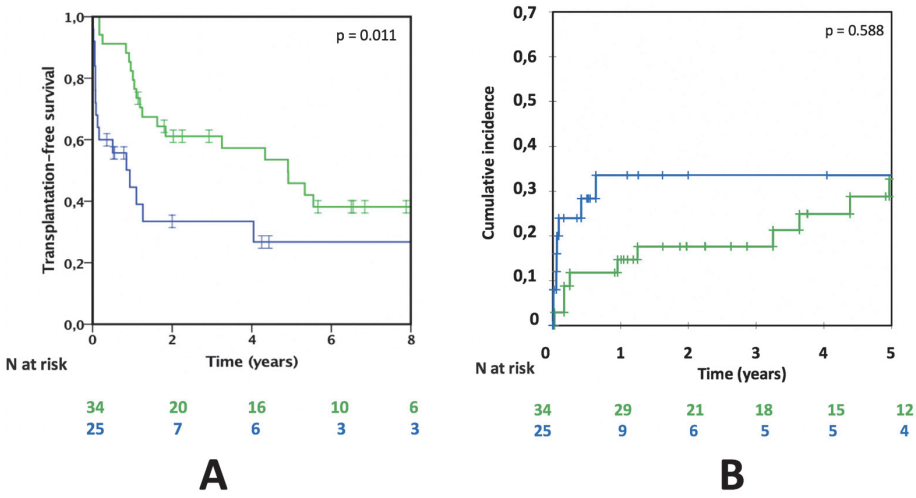

Figure 18. Comparison of transplant-free survival (A) and cumulative incidence of sudden cardiac death (B) between 25 patients with giant cell myocarditis (GCM, blue line) and 34 patients with cardiac sarcoidosis (CS) initially misdiagnosed as GCM (green line)

6 DISCUSSION

6.1 Methodological considerations and limitations

6.1.1 Patient population

When the national MIDFIN registry was launched in 2008, all five university hospitals and 17 central hospitals were contacted with a questionnaire for information on CS and GCM patients in their local registries. Originally, all five university hospitals and six out of 17 central hospitals responded. Due to the rarity of CS and GCM, many central hospitals refer these patients to university hospitals for diagnosis and planning of treatment. As the MIDFIN registry is hospital-based, patients presenting with out-of-hospital SCD and diagnosed with CS at forensic autopsy are initially missed. In the present work, these cases were identified from the national cause-of-death registry and included in the study population. With 351 CS and 29 GCM patients, the present thesis work represents one of the largest reported for both diseases. Adding the cases from the cause-of-death registry improved the representativeness of the cohorts although, in theory, it may also have introduced some reverse survivorship bias into the data. The MIDFIN registry mainly includes patients admitted for clinically manifest and relatively acute cardiac signs and symptoms. Patients with extracardiac sarcoidosis and asymptomatic or minimally symptomatic CS remain largely outside the MIDFIN registry and the present study. Our inclusion criteria adhered to the HRS consensus statement[83] and WASOG diagnostic instrument[84] for diagnosing CS, and an exceptionally large proportion of patients, nearly two thirds, had definite CS, i.e., the diagnosis was based on myocardial histology. The study population represents northern European ancestries only. Ethnic homogeneity is a strength but it can also be taken as a limitation, since it undermines the generalizability of our findings.

With a relatively high autopsy rate, Finland offers a good setting for cause-of-death registry-based studies. From 1998 to 2010, the annual autopsy rate exceeded 30% and in 2015, it was 21%.[334] In comparison, the concurrent autopsy rates were < 20% in other European Union states.[334] The registry search was based on selected ICD-10 codes as well as specific keywords in the text body of the death certificate. Some patients may have been missed by this search protocol. This may be especially true for GCM, as it does not have a specific ICD-10 code. Finally, we had to reject a few cases from the cause-of-death registry where histological material could not be collected for evaluation.

6.1.2 Data collection and analysis

Most of the data presented here was collected retrospectively from available medical documents. The histologic material obtained from autopsy-diagnosed cases, and from each GCM case, were, however, re-reviewed for the present work, as were the CMRI images in Study I. Regarding the cases of CS from the MIDFIN registry, histology was not consistently re-evaluated, but diagnoses made by pathologists in the attending hospitals were relied upon. The CMRI protocols and techniques evolved substantially during the 10-year period covered by Study I. CMRI was utilized less often in diagnostics of unknown cardiomyopathies at the beginning of this period, thus reducing the number of study subjects. In the present study, cardiac death was defined as SCD if prodromal symptoms occurred within 24 hours of death. It was felt that adhering to the strict one-hour definition, commonly used in epidemiological studies, would have been inappropriate for the purposes of this work. Only "hard" endpoints such as fatalities, cardiac transplantations, and life-threatening VAs were collected. Despite the retrospective study design, these endpoints can usually be precisely defined from hospital charts.

From a statistical point of view, the numbers of cases and endpoint events remain rather small. In several cases, some important laboratory or imaging data could not be obtained, further limiting the statistical power of our analysis. Due to the retrospective nature of our studies, only observational remarks can be made on the effects of immunosuppressive and other therapies in CS or GCM.

6.2 Comparison with previous data

6.2.1 Differential diagnostics of cardiac sarcoidosis and giant cell myocarditis

Our audit of all GCM cases in the registries exposed major diagnostic problems as more than half of the GCM diagnoses had to be converted to CS. One of the main reasons was that, in many forensic autopsies, cardiac or extracardiac granulomas had in fact been recognized and reported but the diagnosis was still set as GCM. In other cases, myocardial granulomas had simply escaped detection on microscopy. In postmortem studies in particular, tissue autolysis can impair the quality of histological material and hamper the detection of granulomas. During the original histological review for studies II and III, only myocardial specimens were analyzed, and only basic tissue stains (HE and Masson's trichrome) were used. We found that previously missed granulomas could be discerned using immunohistochemical staining (see Figure 11). In a few cases, diagnostic reclassification was based on detecting sarcoid granulomas in either extracardiac organs or in a cardiac explant examined de novo. Finally, our decision to consider even immature granulomas

diagnostic of CS and exclusive of GCM had a major impact and needs emphasis here. It is of note that in the original works (studies II, III and Kandolin et al.[6]), only unequivocal fully-formed myocardial granulomas were considered diagnostic of CS.

There is no unanimity among experts on whether granulomas can be seen in GCM. Moreover, it remains unsettled whether CS and GCM are truly different entities or if they represent a severity spectrum of one disease. Historically, since the first reported case of GCM in 1905,[109] GCM and CS have usually been conflated when authors described cases of myocarditis associated with giant cells with or without granulomas and varying degrees of myocardial damage. In the 1950s, Tesluk et al. made a distinction between idiopathic GCM and granulomatous myocarditis (the common term in that era, describing what is now recognized as CS) by suggesting that GCM is characterized by a lack of myocardial granulomas and the presence of a diffuse inflammatory infiltrate and multinucleated giant cells.[335] Later in 1975, Davies et al. further promoted the differentiation between these entities by describing GCM cases with serpiginous areas of myocardial necrosis associated with giant cells and florid histiocytic and eosinophilic infiltrates.[68] They concluded that CS was easily differentiated from this form of myocarditis by its easily recognizable granulomas. In another study by Litovsky et al., GCM cases showed extensive infiltrates of eosinophilia, myocytic destruction, lymphocytes of the CD8-type and an absence of granulomas.[35] In contrast, myocardial granulomas were seen in all CS cases and the lymphocytes were predominately of the CD4 type. Also, necrosis and eosinophilia were absent. Macrophagic giant cells were seen in CS cases and myogenic giant cells in the GCM cases.[35] The complete absence of myocardial granulomas was the key differentiating histopathological characteristic in all these studies, as it was in our work, and the landmark report of the Multicenter GCM Study Group[3] also adhered to this diagnostic fundament. Despite this, the very same group later modified their criteria for GCM allowing the presence of granulomas if the extent of myocardial necrosis was "out of proportion" to the amount of granulomas.[4] The group concluded that granulomas and fibrotic changes are more frequent in CS, whereas areas of necrosis, foci of lymphocytic myocarditis, and eosinophilia are greater in GCM. There are reports suggesting that, in GCM, granulomas may also be found in extracardiac organs,[3,35,68,257,335] clouding the distinction even more.

The results of our re-evaluation were highly dependent on the criteria used for GCM exclusion. Had we adhered to the definition by Okura et al.,[4] where granulomas were not absolutely exclusive of GCM, the results would probably have been different. In our work, granulomas of any stage, in or outside the heart, excluded the diagnosis of GCM. Several aspects of both current and previous data call into question the concept of CS and GCM as fully separate entities. First and foremost, a T-cell mediated inflammatory process seems to be a key

pathogenetic factor in both diseases.[33,35,37,54,56] Co-existing autoimmune disorders are equally common in sarcoidosis[49–51,52,53] and GCM.[3] Thymic tumors have been associated with GCM[61–66] but are seen in sarcoidosis as well.[53,336,337] Finally, there are impressive case reports of patients with lung or other organ sarcoidosis having myocardial histology of GCM.[258,259,338]

CS and GCM resemble each other from a clinical perspective as well. Their spectra of cardiac manifestations are highly overlapping (Figure 2). Some differences in the presenting manifestation exist, however, with HF being the most common in GCM[3,4,7] and AVB in CS.[4,7,9] A fulminant manifestation with rapid progression is characteristic of GCM,[3–5,7,251] whereas a prolonged disease course is more typical of CS.[4,7] Still, severe forms of CS with rapid deterioration are reported[170–172] and, conversely, GCM can present with a protracted clinical course.[13,169] In summary, according to our experience and the available data, CS and GCM seem to be either two closely related T-cell mediated myocardites or simply represent different stages or severities of one and the same disease mechanism. In the single-disease hypothesis, GCM would represent an aggressive type of CS confined to the heart. Admittedly, these considerations remain mainly speculative pending more definitive research insight into the pathogenesis of these conditions.

Finally, some methodological aspects of our histopathological analysis deserve a mention. The re-evaluation was made by two experienced cardiac pathologists whose consensus was required for each histological diagnosis. In conducting the review of histology, the pathologists were not fully blinded to the clinical data. The assessment of the extent of myocardial necrosis, fibrosis and eosinophilia was based on a visual estimation on an arbitrary four-point scale. Though subjective and sensitive to differences in interpretation, this method has been used for comparable research purposes.[4,339]

6.2.2 Epidemiology

6.2.2.1 Cardiac sarcoidosis

Regarding the epidemiology of CS, this study is a continuation of the recent thesis by Riina Kandolin.[115] In her work, a significant increase was found in the detection rate of CS in Finland from the late 1980s until 2011. The current work updates the figures for CS diagnosed during life until the end of 2015. A significant addition, however, is the inclusion of cases detected from the national cause-of-death registry (n=61) from a parallel period. These cases represent CS that was either asymptomatic during life or, if symptomatic, escaped correct diagnosis until autopsy. Some data from outside Finland also suggests that the detection rate of CS may be increasing. The number of CS-related hospitalizations and

transplantations in the US have substantially increased since the turn of the millennium.[106,340,341] Improved diagnostics, especially advanced cardiac imaging might, at least in part, explain the increased detection of CS. According to several CMRI studies listed in Table 3, cardiac involvement in sarcoidosis is present in 20–45% of cases.[28,78,89,93–102] Another possibility is that the true incidence of sarcoidosis (and CS) is increasing. However, a Swedish registry-based study did not indicate any change in the number of incident cases of sarcoidosis over a 10-year period up to 2012. In contrast, another recent study, exploring a global database,[342] reported that the age-standardized incidence rate of sarcoidosis showed an increasing trend from 1990 to 2017.[343]

As mentioned earlier, most of the CS patients included here sought medical care for manifest and serious cardiac signs and symptoms. The epidemiological figures reported here do not cover asymptomatic but detectable CS as detailed cardiac screening of patients with systemic sarcoidosis was not common practice in the era our work represents.

6.2.2.2 Giant cell myocarditis

GCM is an extremely rare disease. We detected a total of 29 GCM cases over a 25-year period in Finland. While still few, 29 cases in a population of ≈ 5,500,000 is a conspicuously high number compared to the figures of the Multicenter GCM Study Group[3] for their immensely larger background population. Of note, their landmark paper was based on 63 patients detected from 49 medical centers representing 16 countries worldwide.[3] Caforio et al. reported that, in a 13-year time period, five cases of GCM were identified amongst cases with suspected myocarditis referred to a tertiary center.[113] Another report identified 10 GCM cases from 4738 consecutive patients undergoing EMB in a nine-year period for suspected myocarditis or DCM.[111] A Finnish autopsy study by Kytö et al. found GCM in 5.6% of 142 patients with myocarditis registered as their cause of death, from 1970 to 1998.[114]

6.2.3 Patient characteristics and clinical manifestations

6.2.3.1 Cardiac sarcoidosis

Our series of 351 CS patients showed a clear female predominance (72%). Previous studies have reported both male[4,108] and female[8,10] predominance in CS. The average age at symptom onset of 52±12 years is comparable to earlier reports.[4,8,10,108] The spectrum of different presenting manifestations was also mainly in line with previous data.[4,8,10,108] It has been recognized by our group and others that CS is a frequent cause of seemingly idiopathic AVB in young to middle-aged people.[121,122] As in the earlier MIDFIN registry based study,[115] high-grade AVB was also the most

common main presenting manifestation in this study, being present in almost half of the patients at presentation.

A life-threatening VA, or even SCD from VF, is not rare as the first sign of CS.[4,8,108] In the present work, combining data from clinical and cause-of-death registries, 14% of all 351 patients had SCD as first manifestation of CS and another 14% presented with sustained VT. In two earlier autopsy studies, SCD was the first sign of CS in 11–17% of all cases undergoing postmortem examination.[14,15]

6.2.3.2 Giant cell myocarditis

With a mean age of 57±13, our patients were older than the patients from the Multicenter GCM Study Group reports[3,4] where the mean age was 42.5±13.2 in the full series.[4] In the series of GCM patients surviving > 1 year by Maleszevski et al., a more comparable age distribution, with a mean age at diagnosis of 54.6±14.1 years, was reported.[13] Like in CS, our GCM population showed a female predominance (69%). Previous studies have reported varying sex distributions with both male and female predominance in GCM.[3–5,13,258] Concomitant autoimmune disorders were present in 14% of cases which is comparable to earlier data.[3]

HF with depressed LV function was the most common main presenting manifestation of GCM in this series, being found in almost half of the cases. HF was also the most common first disease manifestation in the studies by the Multicenter GCM Study Group[3,4] and by Maleszevski et al.,[13] being present in 58–75% of cases. An arrhythmic event, sustained VT or SCD, was the first manifestation in one quarter of the patients. This is comparable with the Multicenter GCM Study Group report, where VT was the main presenting manifestation in 29% and VF in 3% of patients.[4] High-grade AVB was found at presentation in 21% of our patients, being more common here than in the earlier study populations.[3,4]

6.2.4 Sudden cardiac death as the mode of death in cardiac sarcoidosis

It is well established that CS predicts a high risk of VAs. The incidence of significant VAs in known or suspected CS varies significantly between studies, with reported rates ranging from 7 to 60% (Tables 8 and 9). Still, no studies have systematically analyzed the frequency of SCD in fatalities from CS. A novel finding of this study was that SCD was the mechanism of death in as many as four out of five fatalities in a nationwide CS population. It should be noted that significant CAD was present at autopsy in six out of the 67 SCD fatalities and its contribution to the fatal event in these cases cannot be decisively determined. An outstanding and provocative observation was that, even after the exclusion of cases with concomitant severe CAD, SCD from previously undiagnosed CS accounted for 64% of all deaths. In over half of these cases, CS had apparently been clinically silent before the fatal event. It is noteworthy, however, that due to the inclusion of autopsy-diagnosed

cases, reverse survivorship bias may have increased the importance of the role of SCD in the present study.

6.2.5 Incidence of life-threatening ventricular arrhythmias in giant cell myocarditis

Prior to this work, no studies have systematically reported the incidence of life-threatening VAs in GCM. In this study, SCD was the mode of death in almost half of the fatalities, outnumbering both HF-related and post-transplant deaths (27% each). The cumulative incidence of life-threatening VAs rose steeply during the first 12 months after presentation, but very few arrhythmic events were seen thereafter (Figure 17B). It is noteworthy that, as cardiac transplantation and death from HF were considered competing events, few patients remained "at risk" after the first year (Figure 17B). The overall cumulative incidence of SCD at one year from symptom onset in this work was 41%. The corresponding figure for any life-threatening VA was 52%. These figures are comparable with earlier reports[3,4] and suggest a very high risk of life-threatening VAs in GCM

6.2.6 Survival

6.2.6.1 Cardiac sarcoidosis

Here, the five-year overall survival figures for all CS patients and for patients presenting with lifetime symptoms were 85 and 93%, respectively. These figures indicate better prognosis than what the studies prior to the turn of the millennium had suggested. In a British study of 250 CS patients from 1986, only 40% were alive five years after symptom onset.[161] In another study of 95 Japanese CS patients,[8] the overall survival after five years was 60% and finally, Okura et al.[4] reported a transplant-free survival rate of 60.5% at five years in CS patients collected from various centers in the US and Japan. More in line with the present results is a recent study reporting a five-year overall survival of 95.5% in 73 CS patients, of whom almost all were given immunomodulatory therapy and more than half received an ICD.[108]

Improved diagnostics and heightened suspicion of CS in the current era may have resulted in earlier diagnosis and detection of more benign forms of CS. Autopsy studies such as the widely-cited work of Roberts et al.,[14] where only 27% of patients were alive at 12 months after onset of symptoms, are obviously biased towards very severe forms of CS. ICD implantation is probably the most important single intervention with a potential to reduce CS related deaths. In this study, 54% patients had an ICD while the respective figures were much lower in reports from the early 2000s.[4,271]

6.2.6.2 Giant cell myocarditis

GCM is commonly depicted as an aggressive disease that very often necessitates cardiac transplantation. The overall survival of our patients presenting with lifetime symptoms was 67% at five years. Survival without cardiac transplantation at five years was 26%. The survival rates reported here are better than those reported by the Multicenter GCM Study Group showing a five-year transplantation-free survival of only 10%.[4] The corresponding figure for their patients diagnosed by EMB was 21.9%.[4]

6.2.7 Predictors of outcome

6.2.7.1 Cardiac magnetic resonance imaging as a predictor for adverse events in cardiac sarcoidosis

We studied the prognostic role of CMRI in a group of 59 patients with myocardial biopsy confirmation of CS in more than half of the cases. In line with previous and later data,[28,30,318,319] the amount of LGE on CMRI was predictive of the study endpoints, mainly consisting of life-threatening VAs. Other findings associated with worse outcome were impaired RVEF and scar-like thinning of the basal septum, both of which have been shown to associate with higher risk in other studies as well.[28,212,310,317] Interestingly, LVEF was not associated with outcome events, highlighting the need for more accurate signals of high risk in CS than depressed LV function.

When mixed sarcoidosis populations, with or without cardiac symptoms, are screened for cardiac involvement, the mere presence of abnormal LGE associates with higher risk.[28,93,94,96,100,212,318–320] The likely explanation is that the presence of LGE on CMRI, a diagnostic criterion for CS,[80,83,84] identifies from such study populations individuals with cardiac involvement. In addition to the present study, only three other works have focused on the predictive role of CMRI in confirmed CS. Ours is, however, hitherto the only CMRI study where CS was diagnosed by the international HRS/WASOG criteria.[83,84] The previous studies[30,307,316] used the JMHW criteria,[81,82] which are known for their issues of inferior sensitivity and specificity (see also section 2.6.1).

6.2.7.2 Prognostic factors in giant cell myocarditis

With no comparable earlier data, a novel aspect of this work was the analysis of outcome predictors in GCM. Markers of severe inflammation and cardiac dysfunction were found to predict transplant-free survival, while the extent of myocardial fibrosis appeared as a particular predictor of SCD and life-threatening VAs. As myocardial fibrosis is a key pathophysiological factor contributing to VAs, it was not surprising that extensive fibrosis correlated with the occurrence of VAs.

Interestingly, LVEF at baseline did not stand out as an independent prognostic factor. Yet, as the numbers of patients and events were limited, these results should be interpreted cautiously.

6.2.8 Comparison of cardiac sarcoidosis mimicking giant cell myocarditis vs. true giant cell myocarditis

As more than half of the cases originally diagnosed as GCM were ultimately deemed as CS, in many cases based on an evolution of previously set histological criteria,[3,4,6,35,68,257] we were interested to find out whether these groups differed in terms of clinical characteristics and survival. The data shows that "true" GCM patients were older, presented more often with HF, had higher cardiac troponins and NT-proBNP on admission, and poorer long-term survival. These differences, and the observation that five-year survival in the group of CS mistaken for GCM was only 46%, imply that the latter cases most likely represented advanced and/or aggressive forms of CS. Importantly, even after adjusting for possible confounders, the histological diagnosis of CS was an independent predictor of a better outcome. It is of note that, for the patients initially diagnosed with GCM, biomarkers of cardiac injury and dysfunction and at least moderate myocardial necrosis or fibrosis retained their prognostic value for transplant-free survival irrespective of the final diagnosis (Study IIb).

Moderate-to-severe fibrosis likewise remained an independent predictor of life-threatening VAs (Study IIIb). An interesting finding was that the cumulative incidence of SCD did not differ between "true" GCM and CS mistaken for GCM (Figure 18B). Since the cohorts in Study V were rather small it remains uncertain whether CS and GCM truly differ in terms of VA risk. As Figures 17B and 18B show, however, the overall absolute risk here was undisputedly significant in both.

6.3 Clinical implications and considerations for future research

The findings of this work underline the fact that, in clinical practice, life-threatening VAs probably constitute the most significant risk of poor outcomes in CS and GCM. In many cases, the cornerstone of care is the recognition of these potentially fatal myocardial diseases as the cause for sometimes unspecific cardiac signs and symptoms. In this study, 24 CS and three GCM patients, escaping a lifetime diagnosis, had cardiac manifestations that, in retrospect, are typical of these diseases. The present findings further underline the importance of considering the possibility of CS (or GCM) in all young or middle-aged patients with an apparently idiopathic high-grade AVB. The results of this work (Study I) and the findings of several other authors[28,30,318,319] also suggest that the quantification of LGE might

help clinicians better stratify the risk of CS. Here, the risk was highest in patients with LGE > 22%, using the full-width at half-maximum method (Figures 10 and 16). The measurement of the extent of LGE is sensitive to the method used,[333] and some other threshold could also be appropriate. Also, the risk most probably is not dichotomic but rather increases with increasing amounts of LGE. Overall, our results suggest that the threshold for early ICD implantation should be kept low in CS and GCM. Although extensive fibrosis on EMB and high cTnT/I at presentation may be seen in GCM patients at the highest risk of VA/SCD, early ICD implantation is probably still warranted in all patients except those with a fulminant disease course where early listing for transplantation is required.

This study shows that the histopathological evaluation of inflammatory cardiomyopathy is demanding and requires a high level of expertise and experience. Immunohistochemistry may be helpful in the diagnosis and detection of immature myocardial granulomas. To differentiate between CS and GCM, every effort should be made not to miss cardiac or extracardiac granulomas. CT findings compatible with lung sarcoidosis and the identification of "hot" extracardiac lymph nodes or other abnormal ^{18}F-FDG organ accumulation on PET should favor the diagnosis of CS. A novel finding of this work was that findings on EMB may have prognostic as well as diagnostic significance. Still, the clinician should probably tailor immunosuppressive therapy to the patient's clinical status and the severity of myocardial injury and dysfunction rather than on histologic findings in a small sample of the myocardium. Lastly, for CS and GCM, the analysis of the cause-of-death registry showed that relying only on the ICD-10 codes and/or initial diagnosis, without further re-evaluation, may give false epidemiological information.

Regarding future research needs, more CMRI studies focusing on confirmed cases of CS are necessary to expand knowledge of the prognostic role of CMRI. In addition to the presence and extent of LGE, other characteristics like its heterogeneity should be focused on in future research. Cardiac imaging studies in GCM are highly anticipated, as current knowledge is based only on case reports. It is difficult to identify, and impossible to prove, the benefits of immunosuppression in either CS or GCM from retrospective observational studies or even from prospective registries. Randomized and controlled trials are needed and are long overdue. As CS and GCM are very rare diseases, such studies are not possible without research collaboration between institutions, hopefully internationally. In addition to clinical studies, basic and translational research is needed to better understand the pathogenesis of CS and GCM and to identify molecular targets for diagnosis and treatment. DNA analyses of large CS populations as well as more focused myocardial gene expression analyses and RNA profiling might be able to contribute in this way. Basic research could also help ultimately settle the issue of whether CS and GCM are different disease entities or parts of a continuum in one and the same inflammatory cardiomyopathy.

7 CONCLUSIONS

1. CS and GCM resemble each other both clinically and histopathologically. Their differentiation on biopsies is sensitive to the microscopic criteria used. CS can be mistaken for GCM if myocardial or extracardiac granulomas are missed or detected but are still perceived to represent GCM. In the present study, CS mistaken for GCM had a better outcome than "true" GCM.

2. The detection rates of both CS and GCM are increasing. The most common clinical presentations are high-degree AVB in CS and symptomatic LV dysfunction in GCM. CS can present during life and escape diagnostic work-up until autopsy due to SCD.

3. In both CS and GCM, an unexpected SCD can be the first and only disease manifestation. Its frequency as a form of presentation was 14% in both cohorts of the present series. SCD dominates the spectrum of fatalities in these diseases. Here, it was the mode of death in 80% of fatalities from CS and in 45% of fatalities from GCM.

4. Although survival appears improved in CS, mortality is still worrying given that the patients are typically working-age individuals. The 10-year survival rate in patients diagnosed during life was 87%.

5. CMRI provides useful information about predictors of outcomes in CS. In the present work, survival free of cardiac transplantation and life-threatening VAs was worse in patients with a higher extent of LGE, lower RVEF, and thinning of the basal LV septum.

6. The prognosis of GCM, a disease once considered inevitably deadly without transplantation, appears more favorable today. Still, the transplant-free five-year survival was no better than 26%, with the overall five-year survival being 67%. These figures are based on more than two decades of experience with GCM in Finland.

7. The present work shows that GCM has a more outstanding arrhythmogenic profile than previously considered. The incidence of life-threatening VAs was highest during the early months with the cumulative incidence of SCD or any life-threatening VA amounting to 52% by the end of the first year from disease onset. The risk of SCD was associated with at least moderate fibrosis on myocardial biopsy and higher circulating cTnT at presentation.

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